Sys Rev Pharm 2021;12(2):119-126
A multifaceted review journal in the field of pharmacy

Analysis of SCN1A polymorphism as Genetic Risk Factor for Neurological Disorders

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ABSTRACT

Epileptic seizures lead to changes in the importance of the blood laboratory tests which represent changes in various systems of organs in the body. A present study assessed the association between the rs3812718 polymorphism in SCN1A gene and susceptibility with epilepsy. In total, 48 subjects (28 patients and 20 controls) were included in the study. Subjects' age and sex were matched. The patients' demographic profiles, including the gender (female: 26 and male; 34), mean of ages (21±8.6), the controls gender (female: 6 and male; 19) and age mean (39±13.3). Single nucleotide polymorphisms (SNPs) was used to investigate the distribution of SCN1A rs3812718 genotypes (G > A) in patients with Epilepsy. Direct sequencing is use to identify the (G>A) polymorphisms of the SCN1A gene on chromosome 2q24. Genotypes and allelic frequencies for the SCN1A in both groups were compared. In addition, the results show two other SNPs for the first time in Iraqi patients rs2217199 T>C and rs3812719 G>T and the study determines some biochemical tests (potassium) were performed by Reflotron and (glucose, sodium, chloride and calcium) by a Spectrophotometer in the sera of subjects. In this population, the alleles frequency of rs2217199/ C, rs3812719/ T, rs3812718/A, the susceptibility of epileptic with gene polymorphisms was correlated (OR = 5.84, p = 0.0001; OR = 4.41, p = 0.001; OR = 5.33, p = 0.001; respectively). The haplotype (CTA) was also significantly related with Epileptic patients (OR = 7.08; p = 0.001). Also, the study showed an increase in glucose levels at p-value= 0.008, normal value in serum K, Cl, Ca and Na levels in Epileptic patient with seizure compare with control. The study in an Iraqi population suggests that SCN1A polymorphisms genetic risk factor for Epileptic patients. Simple blood testing, particularly for some encephalopathies, can be a crucial help for recognizing the etiology.

Keywords: Epileptic seizures, Single nucleotide polymorphisms (SNPs), SCN1A, Haplotype.

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INTRODUCTION

Epileptic encephalopathies are the group of pathological conditions of various etiologies, which are manifested by neurocognitive deficiency and in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function (Engel, 2001). The physiological effects of an epileptic seizure depend on the form; duration and severity of the seizure and the pre-existing status of the patient. Seizures contribute to physiological modifications that are distinctive. The neuroendocrine pathway is incited by maximal neuronal excitation to secrete hormones. Whole body muscle contractions and the release of catecholamines increase the need for muscular, cerebral and cardiac oxygen, while reduced respiration impairs compensatory processes to fulfill this need (Nass *et al*., 2017). In regular clinical practice, electrolyte disruptions are often experienced. Routine laboratory findings are widely used to diagnose these anomalies, and they are not typically of therapeutic importance. However, if neglected or not adequately treated, they may also cause severe complications (Castilla-Guerra *et al*., 2006). Many organs and tissues, including the brain, can be affected by electrolyte irregularities. Much of these derangements' clinical symptoms are primarily neurologic and parallel to the magnitude of neuronal injury. In addition, these conditions can occur with seizures or with increasingly progressive symptoms and signs of neurology, and therefore require emergency care (Rose and Post, 2001; Riggs, 2002). Abnormal glucose levels may cause seizures, whether they are too high or too low. The issue is highly important for people with diabetes whose blood glucose levels can fluctuate significantly over the course of a day due to undercurrent disease, insulin level fluctuations or other metabolic factors (Safstrom, 2003). The term "epilepsy" describes a heterogeneous group of disorders, most of them caused by interactions between several or even many genes and environmental factors (Steinlein, 2008). Good evidence exists to provide analytical risks dependent on the diagnosis of epilepsy syndrome. The research of the molecular cause of epilepsy is now a realistic scientific task and is of clear interest to the patient and the family (Berkovic, 2015). In determining seizure susceptibility, genetic factors appear to play an important role. Around 25 percent of seizure children have a strong family history and seizure agreement in monozygotic twins are between 40-60 percent, but just 10-20 percent in dizygotic twins (Hessel *et al*., 2014). Sodium channels are integral membrane proteins which play a central role in neuronal membrane excitability and action potential generation. Alpha subunit of voltage gated sodium channels encoded by SCN1A, SCN2A and other genes is pivotal for neuronal signaling (Bhat *et al*., 2018). The aim of this thesis was to explore the role of SCN1A gene polymorphism, also, evaluation serum levels of some biochemical tests in patients with Epileptic in Baghdad city.

MATERIALS AND METHODS

Patients and Blood sampling:

Blood was obtained from subjects with an epileptic whose visit to the Neurosciences Hospital in the Baghdad city during the period from November 2019 to January 2020. A combination of clinical criteria and an electroencephalogram are used to diagnose epilepsy patients.. Informed consent was obtained from the patients and controls before the commencement of the study. Blood samples divided into 2 portions: 1 ml of

whole blood is collected into tubes containing EDTA (ethylene demine tetra acetic acid), kept at –20ºC, for genomic DNA extraction, and 2 ml in to gel tubes to obtained serum are separated immediately for biochemical tests.

Biochemical Study:
Glucose, calcium, chloride and sodium were examined by Spectrophotometer Apparatus (Hettich/Germany) which based on the measurement of the intensity of radiation emitted at a wavelength characteristic for a given element. Potassium was examined by Reflotron plus device (Roche/ Germany) which using parameters Reflotron test reagent strips.

Molecular Study:
Using a Norgen DNA extraction kit and the protocol suggested by the manufacturer, genomic DNA was extracted from venous blood (Norgen Biotek, Canada). Extracted DNA was quantified using a Qubit 4 Fluorometer (Thermo Fisher Scientific, USA) Conventional-PCR master mix reaction preparation PCR master mix reaction was prepared by using (2x hot start master) and specific primer(one ml), (IDT Inc., IA) as show in table (1). Primer3 (vraion.0.4.0) software and polymorphic sequence submitted in db. To draw the primers, the SNP database (http:/www.ncbi.nlm.nih.gov / snp) was used to, as show in the table (2). PCR Thermocycler Program: PCR Thermocycler conditions were done by using PCR Thermocycler system as the following, table (3). By Gel Doc (Biorad), amplifications were analyzed on two percent agarose gel stained with ethidium bromide after electrophoresis. PCR products were sequenced using ABI Big Dye v.3.2 terminator sequencing kit (Applied Bio systems). Sequence data were analyzed using Geneious software in comparison to the reference sequence (NCBI RefSeq; http://www.ncbi.nlm.nih.gov).

Table (1): PCR Master Mix Reaction.

Conventional –PCR Master mix	Volume
2x Hot start master mix	0.5 µl
Forward primer (10Pmol/µl)	0.5 µl
Reverse primer (10Pmol/µl)	0.5µl
Template	10.5 µl
Nuclease free water	25 µl

10Pmol/µl: Pico-moles per microliter, µl: Microliter

Table (2): Primers for *SCN1A* Polymorphisms.

Sequence	Primer Sequence
Forward primer	5′TGGCCTTAAATTATGTGAACAA 3′
Reverse primer	5′AACTCTGAATGTTCTCAATGC 3′

Table (3): PCR Profile Program for *SCN1A* Gene.

Step	Temperature	Time	Cycle
Initial denaturation	94ºC	5 minutes	1
Denaturation	94ºC	30 second	20x
Annealing	54.2ºC	1minutes	
Extension	72ºC	30 second	
Final extension	72ºC	7 minutes	1

Statistical analysis
Data processed and analyze by using statistical program social science (SPSS version 13 and WinPepi program). Several statistical tests used to find the significant differences among the studied parameters of patients with seizures epilepsy and control group at (P>0.05) level of significance. The biochemical tests means were compared using the least significant difference at (P>0.05) level of significance, and the results expressed as Mean ± S.D. Chi-square ($\chi 2$) test was used to compare Genotypes and Allele frequencies among the two groups. HWE was assessed for each dataset using the $\chi 2$ value and HWE- P-value. By using SHEsis tools, haplotype-frequencies and linkage disequilibrium (LD) were determined. For all tests, a probability less than (0.05) were considered significant and more than 0.05 was considered non-significant.

Results
In total, 48 subjects (28 patients and 20 controls) were included in the study. Subjects age and sex were matched. Demographic-features of the patients and controls involving gender, age groups family history and mean of ages of subjects are shown in Tables (4).

Table (4): Demographic Characteristics of Epilepsy Patients and Controls.

Groups	Frequency	Percent

Groups (Patients/ Controls)	28/20	58.3%/41.7%
Gender (F/M) : Patients	10/18	43.3%/56.6%
Controls	6/14	30%/70%
Age groups: <12	6	21.4%
(Patient) 13-24	12	42.9%
>25	10	35.7%
Age groups: <12	2	10%
(Control) 13-24	6	30%
>25	12	60%
Family history: Patients	18/10	64.3%/35.7%
(YES/NO) Controls	0/20	0%/100%
Age (mean ± S.D.): Patients	21±8.6	p-value= 0.001
years Controls	39±13.3	

F: Female, M: Male, S.D = Standard Deviation

Biochemical Tests:
Of all patients with epilepsy and healthy without epilepsy served as control whose underwent to the biochemical tests included potassium (K), glucose (Glu), sodium (Na), chloride (Cl) and calcium (Ca) , the resulting , probability value, normal range and units of this test show in the table (5).

Table (5): Chemical Tests for Patients with Epilepsy and Control.

Groups	K	Ca	Cl	Na	Glu
Patient (Mean ± S.D.)	4.7 ± 0.61	2.3 ± 0.2	107.1 ± 6.8	140.9 ± 5.4	128.4± 42.2
Control (Mean ± S.D.)	4.6 ± 0.69	2.4 ± 0.1	105.4 ± 4.1	145.2 ± 5.7	93.9± 13.0
p-value	0.55	0.7	0.29	0.36	0.008*
Normal Range	3.6-5.0	2.1-2.5	95-105	136-145	70-120
Unit	mmol/l	mmol/l	mmol/l	mmol/l	mg/dl

* Significant, S.D = Standard Deviation, p-value= Probability Value, mmol= mill mole, mg= milligram.

Genetic Variation:
DNA Amplification of SCN1A Gene:
Gel electrophoresis analysis using the DNA marker identified the active binding products between the isolated DNA and the unique primers for the SCN1A gene site, and the product size was (bp) for both patients and control groups, and the test were good for both groups.

Genetics Association Analysis:
SNPs were used to investigate the distribution of SCN1A-rs3812718 genotypes (G > A) in patients with Epilepsy. Direct sequencing is used to identify the (G>A) polymorphisms of the SCN1A gene on chromosome 2q24. In addition, the results show two other SNPs for the first time in Iraqi patients rs2217199 T>C and rs3812719 G>T.

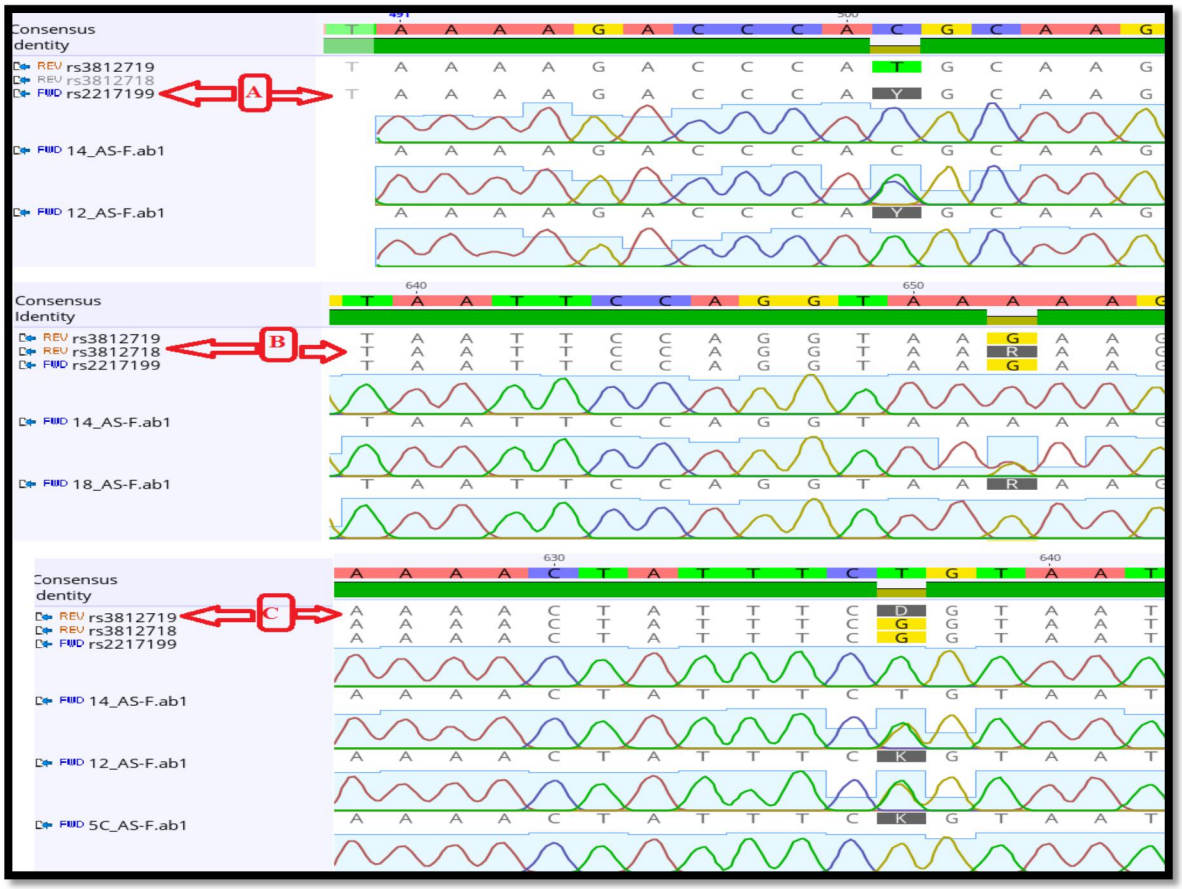
In current study the division of genotypic and frequencies of allelic of the rs2217199 (T>C), rs3812719 (G>T) and rs3812718 (G>A) SNPs in Epileptic patients and controls is shown in table (6). The genotype and allele frequencies between epileptic patients and controls were important in this results for each of the three SCN1A-gene-SNPs analyzed; rs2217199 CC genotypes (p= 0.01, OR= 6.75), rs3812719 TT genotypes (p= 0.01, OR= 5.67) and rs3812718 AA genotypes (p=0.007, OR= 6.54) and allele frequencies; rs2217199 C allele (p= 0.001, OR= 5.84), rs3812719 T allele (p= 0.001, OR= 4.41) and rs3812718 A allele (p=0.001, OR= 5.33), which confirmed the association of these SNPs in the SCN1A gene with an increased risk of epilepsy in the current study to Iraqi population sample.

Table (6): Genotype Distribution and Allele Frequencies of *SCN1A* Polymorphism (rs) when Comparison between Epilepsy Patients and Controls Group.

rs Number of SCN1A Gene	Alleles	Genotypes and Alleles Frequencies	Patient (N=28)		Control (N=20)		Odd Ratio	95% C.I.		p-value
			N	%	N	%		Lower	Upper	
rs2217199	T>C	TT	9	32.1	15	75	0.16	0.04	0.55	0.004
		CT	7	25	3	15	1.89	0.44	8.15	0.32
		CC	12	42.9	2	10	6.75	1.36	33.51	0.01
		T	25	45	33	82.5	0.18	0.1	0.31	0.001
		C	31	55	7	17.5	5.84	2.21	15.42	0.0001
rs3812719	G>T	GG	7	25	12	60	0.22	0.07	0.75	0.016
		TG	7	25	5	25	1	0.27	3.65	0.6
		TT	14	50	3	15	5.67	1.4	22.98	0.01
		G	21	37.5	29	72.5	0.23	0.13	0.41	0.001

		T	35	62.5	11	27.5	4.41	0.398	1.862	0.001
rs3812718	G>A	GG	7	25	13	65	0.18	0.05	0.61	0.006
		AG	6	21.4	4	20	1.09	0.27	4.37	0.5
		AA	15	53.6	3	15	6.54	1.61	26.54	0.007
		A	36	64.3	10	25	5.33	3.21	9.78	0.001
		G	20	35.7	30	75	0.19	0.1	0.34	0.001

N: Frequency, %: Percent, P: Probability



Fifger-1: Genotype Distribution of *SCN1A* Polymorphism (A: rs2217199 T>C; B: rs3812718 G>A; C; rs3812719 G>T) in Epilepsy Patients and Controls Group.

Hardy-Weinberg Equilibrium Test for Case and Control:

The three SNPs of SCAN1A gene were in Hardy-Weinberg equilibrium in the patients group and control as show in, a Table (7). Hardy Weinberg equilibrium of SCAN1A gene shows no significant different between expected and observed in control genotypes (P> 0.05) expect the genotypes in SNP (rs2217199) was significant HWE- P-valu at p= 0.03 as show in Table (7) while in patients group the result showed deviation in the observed genotypes from the expected genotypes (P<0.05), as shown in, Table (7). In the present study, in patients group the result showed the of frequency to wiled genotype (GG, TT and GG) was higher in observes than in expected subjects (25% versus 12.8%; 32.1% versus 20% and 25 versus 14.2), the frequency of heterozygous (AG, CT and TG) genotype was higher in expected than in observed (46.0% vs. 21.4%; 49.8% vs. 7% and 46.8% vs. 25%) and the frequency of mutant genotype (AA, CC and TT) was higher in observed than expected (53.6% vs. 41.2%; 42.9% vs. 30.8% and 50% vs. 39%).

Table 7: Number of (*SCN1A*) Gene Genotypes and their Hardy-Weinberg Equilibrium in Patients and Control Groups.

Groups	SNP	Genotypes	Observed N (%)	Expected N (%)	Chi-squared value	HWE-P value
Patient(n=28)	**rs3812718**	GG	7 (25)	3.6 (12.8)		
		AG	6 (21.4)	12.9 (46.0)	7.96	0.0047
		AA	15(53.6)	11.5 (41.2)		
	rs2217199	TT	9 (32.1)	5.6 (20)		
		CT	7 (25)	13.8 (49.2)	6.838	0.0089
		CC	12 (42.9)	8.6 (30.8)		
	rs3812719	GG	7 (25)	4 (14.2)		
		TG	7(25)	13.1 (46.8)	6.09	0.01

		TT	14 (50)	10.9 (39)		
Control (n=20)	**rs3812718**	GG	13 (65)	11.9 (59.5)		
		AG	4 (20)	7.3 (36.5)	2.5	0.1
		AA	3 (15)	0.8 (4)		
	Rs2217199	TT	15 (75)	13.6 (68)		
		CT	3 (15)	5.8 (29)	4.61	0.03
		CC	2 (10)	0.6 (3)		
	rs3812719	GG	12 (60)	10.5 (52.5)		
		TG	5 (25)	8.0 (40)	2.7	0.09
		TT	3(15)	1.5 (7.5)		

HWE-P value: Hardy-Weinberg Equilibrium-Probability value, N: Frequency, %: Percent

Linkage Disequilibrium (LD) Tests and Haplotype Analysis:

The linkage imbalance was established among the three (3) SNPs of the SCN1A gene (values of LD: 81%, 100% and 58%) figure (2). There was a linkage disequilibrium with the following pairwise parameters between the SNPs: rs2217199, rs3812719: D' = 0.818, r2 = 0.74; rs2217199, rs3812718: D' = 1.000, r2 = 0.68; rs3812719, rs3812718: D' = 0.584, r2 = 0.57 as show in table (8). With a mean probability of 0.03, the phases of the three-SNP haplotypes were statistically reconstructed. On the basis of these results, we were involved in doing a haplotype study in Epileptic patients with evidence from these polymorphisms and the control table (9). In our population, eight distinct haplotypes were identified; the most prevalent haplotypes were CTA haplotypes, comprising 51.7% of total haplotypes in epileptic cases, while TGG haplotypes were the most common in the controls, comprising 67.3% of total haplotypes.

Table (8): Linkage Disequilibrium Tests to Three SCN1A gene SNPs in Epileptic Groups.

D' (r^2)	**rs3812719**	**rs3812718**
rs2217199	0.818 (0.74)	1.000 (0.68)
rs3812719	-	0.584(0.57)

r^2: R squared

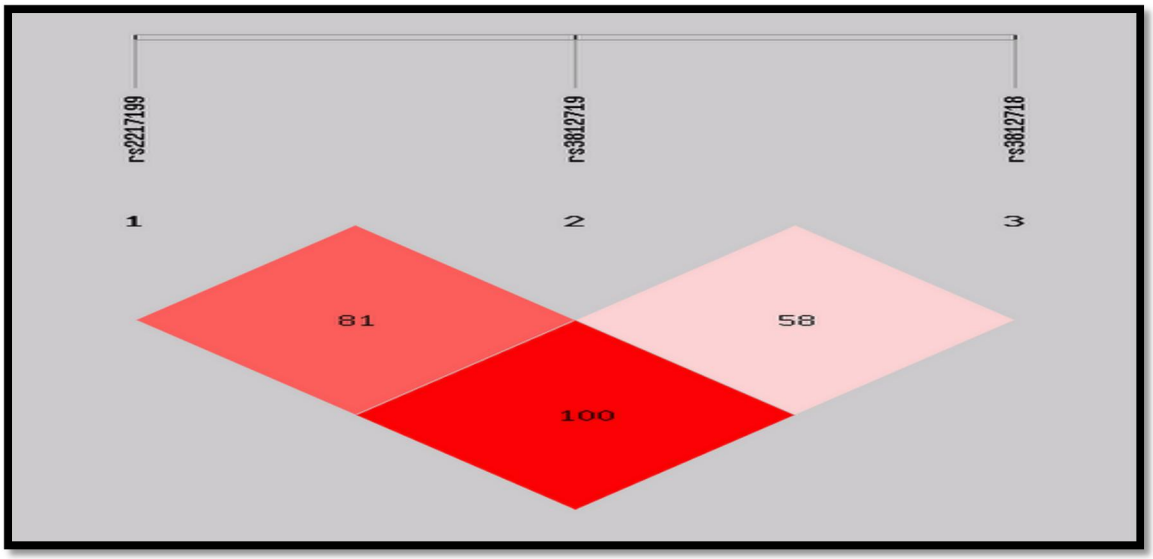


Fig. 2: SCN1A SNPs linkage disequilibrium exam. Using SHEsis software, haplotype frequencies and linkage disequilibrium (LD) were calculated. A value of D 0 of 100 indicates a total LD between two markers and a value of D 0 of 0 indicates a complete balance of the linkage. The darker the cell, the greater the imbalance between the SNPs in the linkage. Rs2217199 (T > C); G > T (rs3812719) and G > A (rs3812718).

Table 9: Haplotype Epileptic and Regulation Frequencies of Three SCN1A SNPs.

Haplotype	Case: n(freq)	Control: n(freq)	Chi2	p-valu	Odds Ratio [95%CI]
C G G	0.00(0.000)	1.07(0.027)	-	-	-
C T A*	28.89(0.516)	4.96(0.124)	14.564	0.001	7.087 [2.408~20.859]
C T G	0.00(0.000)	0.97(0.024)	-	-	-
T G A*	3.96(0.071)	1.02(0.025)	0.872	0.35	2.767 [0.301~25.455]
T G G*	14.93(0.267)	26.91(0.673)	17.921	0.002	0.149 [0.060~0.373]
T T A*	1.04(0.019)	4.02(0.101)	3.393	0.06	0.159 [0.018~1.438]
T T G*	5.07(0.091)	1.05(0.026)	1.469	0.22	3.497 [0.410~29.802]

C G A*	2.11(0.038)	0.00(0.000)	1.464	0.22	-

DISCUSSION

Epilepsy is one of the most prevalent neurological diseases, with an incidence per year of 50-120/100,000 people (Wirrell, 2013). In the present study, level of biochemical markers (K, Ca, Cl, Na and Glucose) was estimated. The mean values of serum potassium in epilepsy cases and controls were 4.7 ± 0.61 and 4.6 ± 0.69 respectively, mean values of serum calcium in epilepsy cases and controls were 2.3 ± 0.2 and 2.4 ± 0.1 respectively, mean values of serum chloride in epilepsy cases and controls were 107.1 ± 6.8 and 105.4 ± 4.1 respectively. In our study, there were non-significant variation in potassium, calcium and chloride levels between the patients and healthy individuals**.** This results agreement with Gao *et al*., in 2005, there were no significant differences in the serum levels of potassium, chloride, and calcium between the seizure and control groups (Gao *et al*., 2005). In addition, the mean values of serum sodium in epilepsy cases and controls were 140.9 ± 5.4 and 145.2 ± 5.7 respectively. Sodium level there is lower compared with control but, this lower in serum level of sodium is non-significant. This results agreement with Salehiomran in 2018, in this study, mean serum sodium levels were 136, 134 and 137.3 meq / l in patients with epilepsy seizure, complex epilepsy seizure and control group , respectively ($p<0.05$), and blood sodium levels had no statistically significant effect on epilepsy seizure frequency. As well, In two other studies, Hugen *et al.* in 1995, and Nickavar *et al.* in 2009 it was indicated that serum sodium levels in patients with repeated epilepsy were slightly lower than in patients without recurrence (Hugen *et al*., 1995, Nickavar *et al*., 2009; Salehiomran, 2018). Also, this study is a systematic attempt to test the risk of acute symptomatic seizures based on different levels of glucose of the patients. The mean values of serum glucose in epilepsy cases and controls were128.4± 42.2 and 93.9± 13.0 respectively there is statistically higher significant in serum glucose in epilepsy cases compare controls. Its agreement with studies by Kiviranta *et al*., in 1995 the effects of seizures and fever on complex epilepsy seizures and blood glucose concentrations were studied in four separate patient groups: febrile and non-febrile patients, with and without seizures (Kiviranta *et al*., 1995).

Epilepsy and other diseases have been involved in hereditary variables (Monastiriotis *et al.,* 2012; Nowak *et al.,* 2013; Alkharfy *et al.,* 2013). Epilepsy is a widespread and very heterogeneous neurological condition in which genetics play a significant etiological function, mostly whether the root cause of epilepsy is hereditary or because chromosomes are vulnerable to an epileptogenic insult (Poduri and Lowenstein, 2011). The gene SCN1A is widely studied. The SCN1A gene has reported over 500 mutations, some of which are associated with the generation of epileptic seizures such as febrile seizures, generalized febrile seizure epilepsy plus, or extreme myoclonic epilepsy (Schlachter *et al*., 2009; Lossin, 2009). In the present study, the role of alterations in sodium channel genes *SCN1A* in epilepsy disease was analyzed. We studied two genetic polymorphisms, *SCN1A* in epilepsy disease. The rs3812718 functional SNP leads to the alternate splicing of SCN1A exon 5 found in brain tissue. Two alternate spliced forms of exon 5, a neonatal (5N) and an adult form (5A) that are co-expressed in the adult brain, have been identified in genomic DNA. Latest studies also shown that in individuals with epilepsy, SCN1A IVS5-91 rs3812718 G > A polymorphism affects the proportions of adult and neonatal mRNA transcripts. Therefore, the G allele requires both forms to be expressed, while the A allele greatly decreases the 5N form's expression in comparison to the 5A form. In comparison, up to 50 percent of the transcripts contain the 5N form in persons with the G / G genotype, whereas the A / A genotype allows an undetectable amount of the 5N form to be expressed. In this data showed that the SCN1A IVS5-91 rs3812718 G>A polymorphism might be associated with generalized epilepsy. The presence of A/A genotype could be a risk factor for generalized epilepsy. There was a significant difference in the genotypic distribution of rs3812718 polymorphism between epilepsy patients and control subjects ($p= 0.007$) and the percentage frequency to AA (53.6 %) genotypes. While the percentage frequency to AG (21.4%) and GG (25%) genotypes and allele frequencies to allele A (64.3 %) high than allay G (35.7%). A recent studies that support this data publish by Zhi *et al*., Angelopoulou *et al*., and Tang *et al.* SCN1A IVS5-91 rs3812718 G > A polymorphism has been proposed to be a risk factor for epilepsy because this polymorphism contributes to a mutation in the splicing region, which allows three amino acids to be substituted simultaneously (Tang *et al*., 2014; Angelopoulou *et al*., 2017; Zhi *et al*., 2018). As well, Abe *et al.,* significant association between the rs3812718 AA genotype and epilepsy susceptibility, was identified in Japanese patients (Abe *et al.,* 2008). On the other hand, Studies that disagree this data, published in 2014 to Baum *et al*., the meta-analysis of epilepsy patients supported the association and found a protective effect of the G allele and GG genotypes on the risk of epilepsy (Baum *et al.,* 2014). In addition, a significant in the genotypic distribution of rs3812719 polymorphism in epilepsy patients at ($p=0.01$) to genotypes TT (50%) compare with control. While the percentage frequency to TG (25%) and GG (25%) genotypes and allele frequencies to allele T (62.5%) high than allay T (37.5%). Also, a significant difference in the genotypic distribution of rs2217199 polymorphism between epilepsy patients and control subjects ($p=0.01$), and the percentage frequency to CC (42.9 %) genotypes. While the percentage frequency to CT (25%) and TT (32.1%) genotypes and allele frequencies to allele C (55.0%) high than allay T (45.0%). As for polymorphism of SCN1A gene (rs3812719 and rs2217199), the studies worldwide may be limited about this polymorphism of rs3812719 and rs2217199, and not found any previous studies have been conducted regarding this polymorphism in Iraq population. As well, the current study considers is the first study that suggests associated between the risk of epilepsy and rs3812719 (G>T) and rs2217199 (T>C) of SCN1A gene. Three identified single nucleotide polymorphisms were shown in the variance study of the SCN1A gene. This study chose these, three SNPs; rs3812719 (chr2:166053049), rs3812718 (chr2:166053034) and rs2217199 (chr2:166053185) to test of them in patients in the Iraqi population and estimating the frequency of haplotypes as shown in Table 9. Using SHEsis, the CAT haplotype incidence in patients is slightly higher by 51.7 percent than that measured at p-valu= 0.001 in the control population. In these patients with epilepsy, this haplotype of SNPs was in a homozygous condition and was considered a putative haplotype associated with the disease (Fig. 2). Reported

about haplotype (CAT) in a patient with epilepsy (Pharmacoresponsive patients (n=2) and Pharmacoresistant patients, n=5)) by Hilger *et al*., 2012 (Hilger *et al*., 2012). Appearing the haplotype clarify this through, many correlations assigned to common variants are likely due to some unusual variants, which often occur by chance more frequently with one allele of a nearby common SNP than with the other allele, according to the principle of 'synthetic associations' (Ufer *et al.,* 2009).

CONCLUSION

The study shows that SCN1A polymorphisms are a genetic risk factor for epileptic patients in the Iraqi population and the CTA haplotype was also significantly associated with risk of Epileptic in patients, this result was proven for the first time in Iraq.

Acknowledgments

This work was supported by neurosciences hospital, Baghdad, Iraq, and we appreciate the support of University of Baghdad, Collage of Sciences and the Department of Biotechnology

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding: Self-funding

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