Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/15992
DOI URL: http://dx.doi.org/10.21474/IJAR01/15992

RESEARCH ARTICLE

EFFECT OFVARIATIONSIN ABCC2, CYP2C9, CYP2C19 & SCN2A GENESON TREATMENT RESPONSETO ANTICONVULSANTS- A SYSTEMATIC REVIEWAND META-ANALYSIS OF GENETIC ASSOCIATION STUDIES

Mamillapally Loukya[1], Defria Zeneth B.[1] and Samuel Gideon George P.[2]

1. Doctor of Pharmacy, KrupanidiCollege of Pharmacy, Bengaluru - 560035.
2. Assistant Professor,Department of Pharmacy Practice, Krupanidhi College of PharmacyBengaluru - 560035.

Manuscript Info

Manuscript History
Received: 05 November 2022
Final Accepted: 09 December 2022
Published: January 2023

Key words:-
ABCC2, CYP2C9, CYP2C19 & SCN2A,Genetic Polymorphisms, Drug Resistance, Treatment Failure, Recurrence

Abstract

Objective: This study was aimed to determine the effect of genetic polymorphisms (non-synonymous, missense, and copy number variations) in ABCC2, CYP2C9, CYP2C19&SCN2A genes on treatment response to anticonvulsants.

Methods: The search was carried out in PubMed, Scopus, Cochrane Central Register of Controlled Trials, Embase, LILACS, Google Scholar, MEDLINE, ScienceDirect, Web of Science, and the DOAJ database. Hardy Weinberg Equilibrium (HWE), New-Castle Ottawa scale value, Cochrane Review Manager 5.0 (&R 4.0.3,) and Rayyan QCRI are used for assessing data synthesis, risk of bias, heterogeneity assessment using $I^{[2]}$statistics and calculating Inter-rater agreement respectively. Publication bias assessment was performed using Egger's test and the Funnel plot. For statistical analysis, random effects modeling was used to explain the association between genetic variations in ABCC2, CYP2C9, CYP2C19 & SCN2A genes related to drug resistance or treatment failure.

Results: This meta-analysis includes a total of 29 studies. We found a greater risk of AED resistance in ABCC2rs2273697 genetic variations (OR=1.51 [0.93-2.47], p value=0.03 at 95% CI), ABCC2 rs3740066 genetic variation has a greater possibility of AED resistance was seen in pooled population (OR= 0.85 [0.12-5.85], p-value<0.01 at 95% CI), risk of drug resistance was increased by ABCC2 rs717620 polymorphism. (OR =2.13, [1.02-4.44], p-value<0.01 at 95% CI), CYP2C9 rs1799853 polymorphism had a significant increase in AED resistance (OR =1.27, [0.49-3.32] p-value<0.01 at 95% CI), CYP2C9 rs1057910 polymorphism. (OR= 0.74, [0.32-1.70] p-value 0.01 at 95% CI), CYP2C19 rs4244285 polymorphism. (OR= 0.68, [0.29-1.62], p value=0.02 at 95% CI), SCN2A rs2304016 polymorphism. (OR= 1.20, [0.48-3.05], p value<0.01 at 95% CI), SCN2Ars17183814 polymorphism. (OR =1.51, [1.12-2.03], p value=0.30 at 95% CI).

Conclusions: Gene polymorphisms play a key role in epilepsy development and therapeutic efficacy, and could have greater impact treatment outcomes.

Corresponding Author:- Mamillapally Loukya
Address:- Doctor of Pharmacy, KrupanidiCollege of Pharmacy, Bengaluru - 560035.

……..

Introduction:-

International League Against Epilepsy (ILAE) defines epilepsy as a brain illness characterized by at least two unprovoked seizures occurring within 24 hours of each other[1].Epilepsy is one of the most common neurological diseases, according to the World Health Organization (WHO), with over 50 million individuals suffering from it globally[2],[3].It affects people of all ages and has a significant impact on the morbidity and mortality of those who suffer from it and it may be caused by geneticvariations[4]. Epilepsy is a complicated disorder in which resistance to anti-epileptic drugs (AED) is thought to be influenced by environmental variables, genetic factors, andorboth[5].Anti-epileptic drug (AED) non-responsiveness is a prevalent problem in epilepsy treatment[6]. Anti-epileptic medications (AEDs) are available in clinical practice, however around a third of epilepsy patients remain resistant to treatment[1],[2],[5],[7]. Anti-epileptic drugs (AEDs) suppress neuron development, reduce excitement, and prevent abnormal burst firing. Treatment failure occurs in 30–40% of patients, regardless of personalized dose or the use of a wide range of anti-epileptic drugs[8],[9],[10],[11]. At numerous stages of drug absorption, distribution, metabolism, excretion, and drug concentration at target sites, genetic variations might affect an individual's reaction to therapy[12]. The anticipated effects of AEDs can be predicted using polymorphic genes encoding drug targets and drug-metabolizing enzymes. Genetic variation is a primary factor influencing a patient's individualized response to pharmacological therapy[13]. The drug transporter hypothesis is a basic theory that claims that multi-drug transporter failure on the blood-brain barrier (BBB) influences medication uptake in the brain, including various AEDs[5],[7]. Overexpression of ATP-binding cassette (ABC) efflux transporters at the blood-brain barrier (BBB) is one possible mechanism for lowering AED accumulation, bioavailability, and concentration at seizure foci or their target sites, and a change in the composition and capability of voltage-gated ion channels or neurotransmitter receptors leads to reduced target sensitivity in epileptogenic brain tissue[1],[2],[7],[8],[10],[14],[15]. Most anti-epileptic drugs' dose-plasma concentration relationship is influenced by the activity of drug-metabolizing cytochrome P450 (CYP) enzymes, which may contribute to treatment resistance or side effects[4]. Recent evidence suggests that genetic factors like polymorphisms in the genes of microsomal enzymes involved in drug metabolism (CYP) play an important role in the development of treatment resistance epilepsy[16]. Valproic acid(VPA) is the most commonly used drug for the treatment of epilepsy. Inter-individual variation in VPA dose and plasma levels may reflect the functional repercussions of genetic differences in gene-generatingdrug-metabolizing enzymes[17]. It is processed mainly through phase II metabolism catalyzed by uridine 5-diphosphate-glucuronosyltransferase enzymes (UGT) in the liver[18].

Materials And Methods:-

Ethical Approval

The study was permitted to be carried out at the site by the Krupanidhi College of Pharmacy (KCP), Bangalore. The study protocol was approved by the institutional ethics committee of KCP (Approval no: REF: IEC/KCP/2020-21/03). Clinical data of the patients who fulfilled the inclusion criterion were documented from a pre-designed electronic data capture form.

Searches

Electronic databases including PubMed, Scopus, Cochrane Central Register of Controlled Trials, Embase, LILACS, Google Scholar, MEDLINE, ScienceDirect, Web of Science, and DOAJ will be searched for observational studies reporting genetic association and meeting the inclusion criterion.

Condition being studied

Anticonvulsant failure/recurrence of seizure episodes in patients with generalized/focal seizures.

Inclusion Criterion

Patients diagnosed with generalized or focal seizures and received either one or moreof the following anticonvulsant(s): Acetazolamide, Benzodiazepines, Carbamazepine,

Ethosuximide, Felbamate, Gabapentin, Lamotrigine, Levetiracetam, Oxcarbazepine,Phenobarbital, Phenytoin, Pregabalin, Primidone, Tiagabine, Topiramate, Valproic Acid, Vigabatrin, Zonisamide.

Exclusion Criterion
Review papers, randomized control trials, and unrelated epileptic studies were excluded from the first review of the literature search results.

Intervention or Exposure
Genetic Variations in ABCC2 gene: rs2273697, rs3740066, rs717620.
Genetic Variations in CYP2C9 gene: rs1799853, rs1057910.
Genetic Variations in CYP2C19 gene: rs4244285.
Genetic Variations in SCN2A gene: rs2304016, rs17183814.

Comparator/Control
Patients who are carriers of wild-type variants of ABCC2, CYP2C9, CYP2C19& SCN2A.

Types of study to be included
Case-control and cohort observational studies reporting genetic association will be included.

Main outcome
The recurrence of seizure episodes will be used as a dichotomous outcome measure of treatment response to anticonvulsants.

Measures of effect
Crude odds ratio and Adjusted odds ratio with confidence interval.

Data extraction
Two independent reviewers will screen the quality of retrieved articles. Studies with an inter-rater reliability of more than 90% will be included in the analysis. Patient demographics, clinical characteristics, effect allele frequencies, mean allele frequencies, odds ratios/relative risk, confidence intervals, and type of sequencing will be extracted from each study. Two independent reviewers will extract data from selected literature into a designed electronic data capture form. Discrepancies will be reviewed by a third reviewer and resolved by consensus.

Statistical Analysis
Initial methods of data synthesis included the assessment the of Hardy Weinberg Equilibrium (HWE) value after which the New-Castle Ottawa scale is used for assessing risk bias and Inter-rater agreement was calculated using Rayyan QCRI. The heterogeneity assessment using I^2 statistics was performed by using Cochrane Review Manager 5.0 and R 4.0.3. Publication bias is assessed by using Egger's test as well as the Funnel plot. For statistical analysis, random effects modelling was used to explain the association between genetic variations in ABCC2, CYP2C9, CYP2C19&SCN2A genes related to drug resistance or treatment failure.

Results:-

Eighteen thousand and forty-six records were identified through database search using the keywords ABCC2, CYP2C9, CYP2C19 &SCN2A genetic polymorphisms, drug resistance, treatment failure, recurrence, and anticonvulsant. After applying the exclusion criteria, 36 studies were eligible for inclusion in the systematic review (see Fig: 1). Based on the New Castle Ottawa scale for risk of bias assessment above 36 studies were incorporated in these meta-analysis. Finally, 36 studies were included: 9 studies (n=4,155) assessed the association between the ABCC2 gene and anticonvulsant treatment, 5 studies (n=763) assessed the association between CYP2C9 and CYP2C19 gene and anticonvulsant treatment, 11 studies (n=4,288) assessed the association between SCN2A gene and anticonvulsant treatment.

The studies included in the meta-analysis were conducted in China (n=8), India (n=4), Germany (n=3), Japan (n=1), Malaysia (n=2), Jordan (n=2), Croatia (n=1), Turkey (n=1), Mexico (n=1), Egypt (n=1), Pakistan (n=1),Bosnia and Herzegovina (n=1). Of the 29 articles included in the meta-analysis 11 assessed the pediatric population, 1 assessed the elderly population of16-65 years, 2 assessed 12-40 years, and the remaining 15 articles did not assess any specific age group.

Each study adopted different methods to identify the patient population which included medical records, health insurance databases, and general practice databases

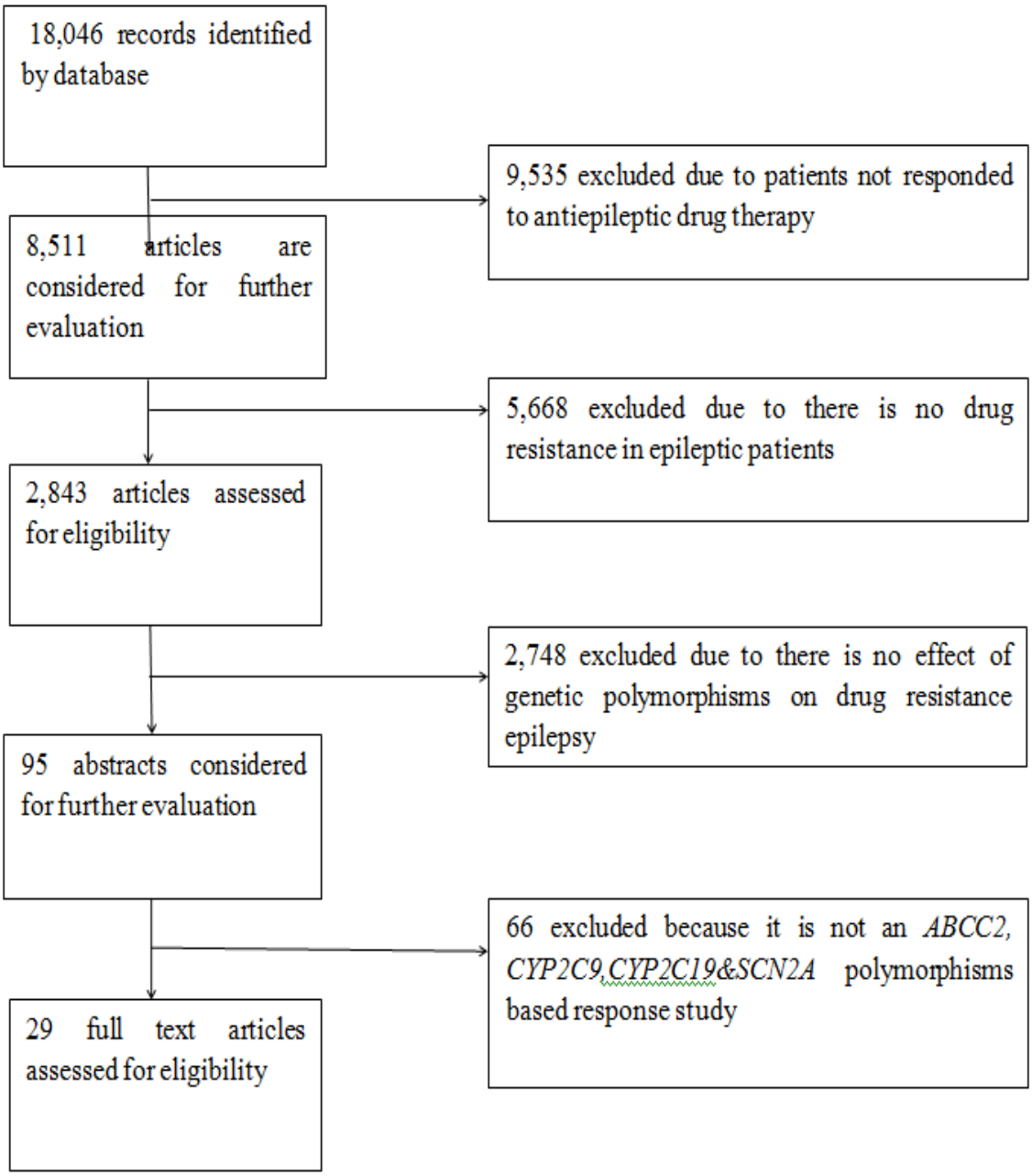

Fig 1:- PRISMA Flowchart for inclusion of articles in systematic review and meta-analysis.

Assessment of quality of the studies:

The quality of the articles included in the study was evaluated using the New Castle Ottawa Scale as recommended by the Cochrane Handbook. This scale assessed the quality of methods used in the selection, comparability of cases and control, exposure in case-control, and outcome in case-control. Each study was rated and awarded a maximum of nine stars. The studies were independently reviewed by three reviewers and any discrepancies were resolved by discussions.

The articles were reviewed using a web application Rayyan QCRI, a tool designed for collaboration to create systematic reviews. The review was conducted for each polymorphism: ABCC2 rs2273697 (see Fig:), ABCC2 rs3740066 (see Fig:), ABCC2 rs717620 (see Fig:), CYP2C9 rs1799853 (see Fig:), CYP2C9 rs1057910 (see Fig:), CYP2C19 rs4244285 (see Fig:), SCN2A rs2304016 (see Fig:),SCN2A rs17183814 (see Fig:) based on this inclusion

and exclusion criteria, New Castle Ottawa assessment, the list of studies to be included in the systematic review was finalized.

Table 1:- Risk of assessment bias by using the New Castle Ottawa scale.

Author	Q1	Q2	Q3	Q4	Q5		Q6		Q7	Q8	NOS score
					a	b	a	b			
D Sporiset al. (2013) [2]	*	*	*	*	*	*	*	*	*	*	10
J Chen et al. (2018) [32]	*	*	*	*	*	*	*	*	*	*	10
J Chen et al. (2018)[16]	*	*	*	*	*	*	*	*	*	*	10
J Qu et al. (2012)[3]	*	*	-	*	*	*	*	*	*	*	9
M Uferet al. (2011) [21]	*	*	*	*	*	*	*	*	*	*	10
M Uferet al. (2009)[5]	*	*	-	*	*	*	*	*	*	*	9
L N AL-Eitan et.al (2019) [26]	*	*	*	*	*	*	*	*	*	*	10
P Kwan et al. (2008)[18]	*	*	-	*	*	*	*	*	*	*	9
L Zhou et al. (2015)[9]	*	*	-	*	*	*	*	*	*	*	9
M Liu et al. (2020)[31]	*	*	*	*	*	*	*	*	*	*	10
L Shi et al. (2019)[31]	*	*	*	*	*	*	*	*	*	*	10
R Lakhan et al. (2009)[28]	*	*	*	*	*	*	*	*	*	*	10
R Kumari et al. (2011)[12]	*	*	*	*	*	*	*	*	*	*	10
L Shi et al. (2019) [29]	*	*	*	*	*	*	*	*	*	*	10
H R Nazishet al. (2018)[10]	*	*	*	*	*	*	*	*	*	*	10
M Seven et al. (2013)[20]	*	*	*	*	*	-	*	*	*	*	9
N Pejanovic-Skobic et al. (2019)[12]	*	*	-	*	*	*	*	*	*	*	9
M Makowskaetal.(2020)[23]	*	*	-	*	*	-	*	*	*	*	8
M A Lopez-Garcia et al. (2017)[34]	*	*	*	*	*	*	*	*	*	*	10
S Eltalal et al. (2020)[33]	*	*	*	*	*		*	*	*	*	10

Heterogeneity assessment:

Heterogeneity was assessed by visual representation of forest plots and the fraction of variance that is due to heterogeneity was estimated using I^2 statistics.

Seven articles contained the data to compare the drug-responsive population (n= 729) and drug non-responsive population (n=652) to assess the effect of ABCC2 rs2273697 polymorphism associated with treatment failure (Fig:2). An higher risk of AED resistance was observed with ABCC2 rs2273697 genetic variation. (OR 1.51 [0.93-2.47], p=0.03, at 95% CI).

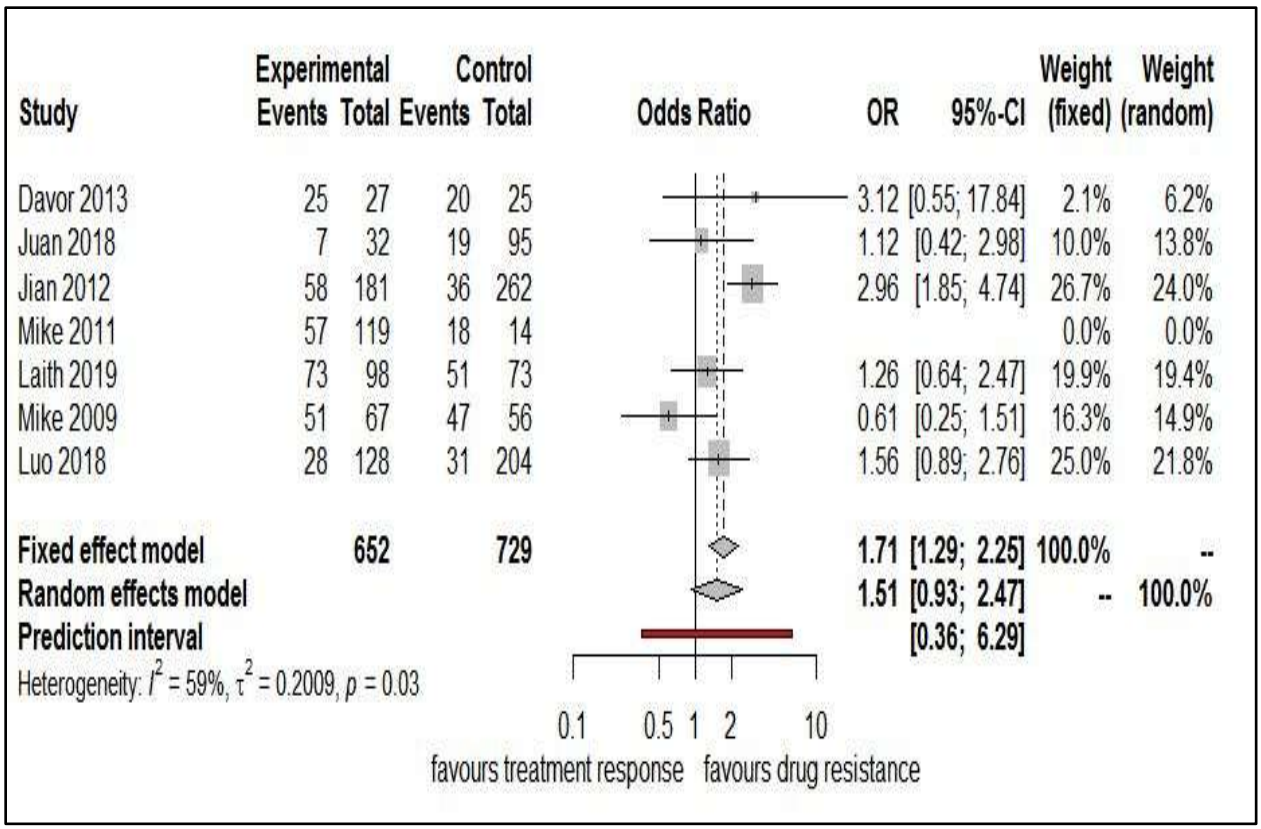

Fig2:-Risk of drug resistance with ABCC2 rs2273697 polymorphism with drug-responsive vs drug non-responsive.

Four articles contained the data to compare the drug-responsive population (n= 338) and drug-non-responsive population (n=299) to assess the effect of ABCC2 rs3740066 polymorphism associated with treatment failure (Fig: 3).A statistically significant association between ABCC2 rs3740066genetic variants shows a higher rise of AED resistance from the pooled population. (OR= 0.85,[0.12-5.85], p=<0.01, at 95% CI).

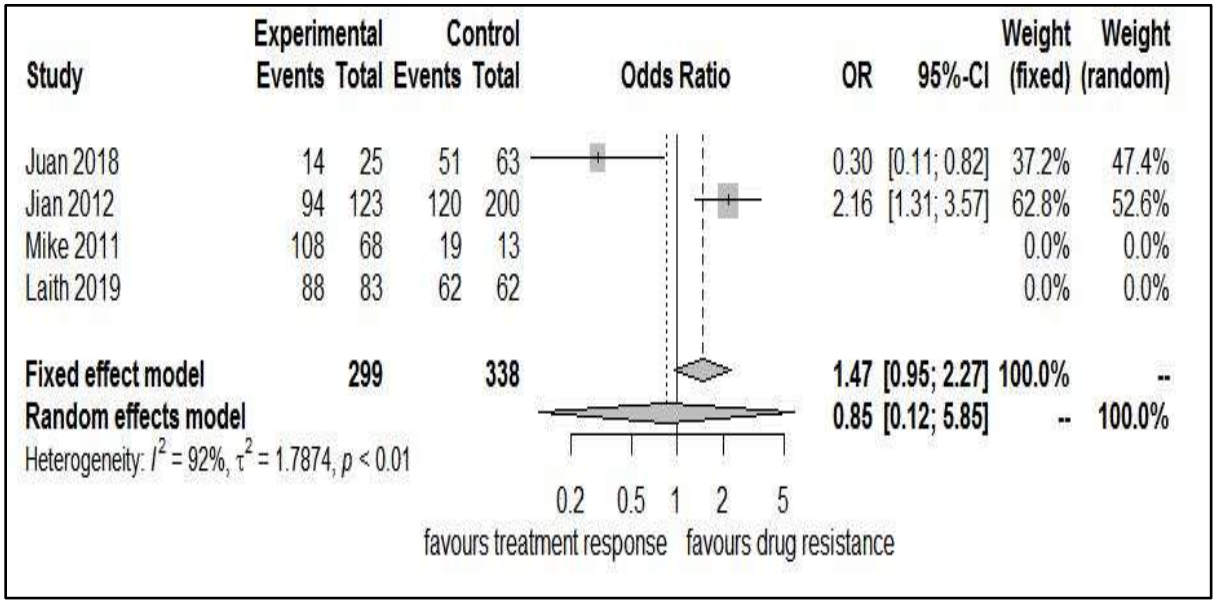

Fig3:- Risk of drug resistance with ABCC2 rs3740066 polymorphism with drug-responsive vs drug non-responsive.
Six articles contained the data to compare the drug-responsive population (n= 566) and drug-non-responsive population (n=554) to assess the effect of ABCC2 rs717620 polymorphism associated with treatment failure (Fig:4).

ABCC2 rs717620 genetic polymorphism causes a greater risk of drug resistance. (OR=2.13,[1.02-4.44], p=<0.01 at 95% CI).

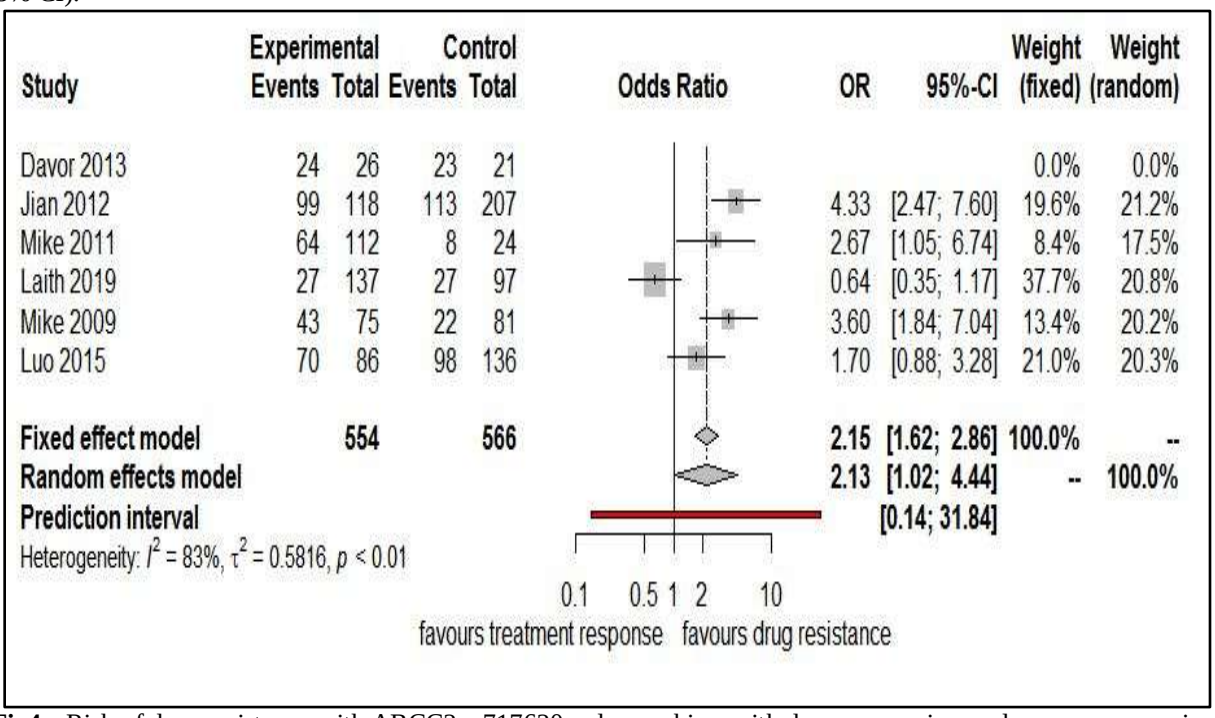

Fig4:- Risk of drug resistance with ABCC2 rs717620 polymorphism with drug-responsive vs drug non-responsive.

Six articles contained the data to compare the drug-responsive population (n= 706) and drug-non-responsive population (n=462) to assess the effect of CYP2C9 rs1799853 polymorphism associated with treatment failure (Fig:5). Genetic variation ofCYP2C9 rs1799853causes higher risk of AED resistance. (OR=1.27 ,[0.49-3.32], p=<0.01 at 95% CI)

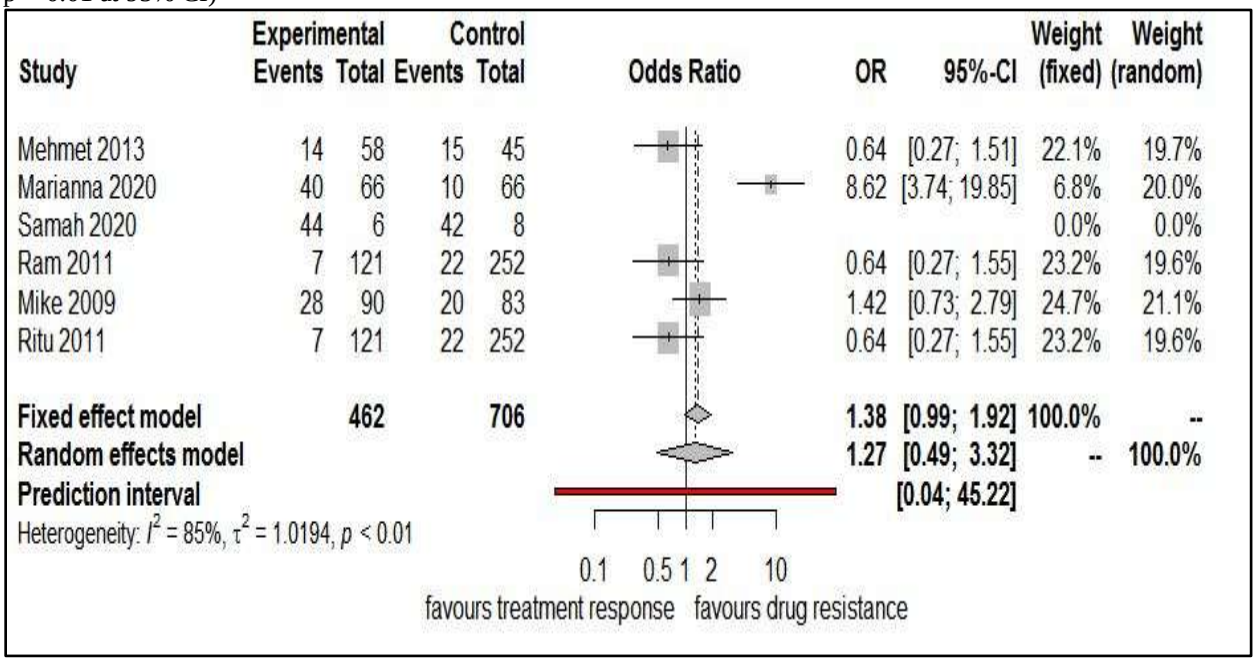

Fig5:- Risk of drug resistance with CYP2C9 rs1799853 polymorphism with drug-responsive vs drug non-responsive.

Five articles contained the data to compare the drug-responsive population (n= 557) and drug-non-responsive population (n=376) to assess the effect of CYP2C9 rs1057910 polymorphism associated with treatment failure

(Fig:6). A higher rise of AED resistance was observed with CYP2C9 rs1057910 polymorphism. (OR=0.74,[0.32-1.70], p=<0.01 at 95% CI)

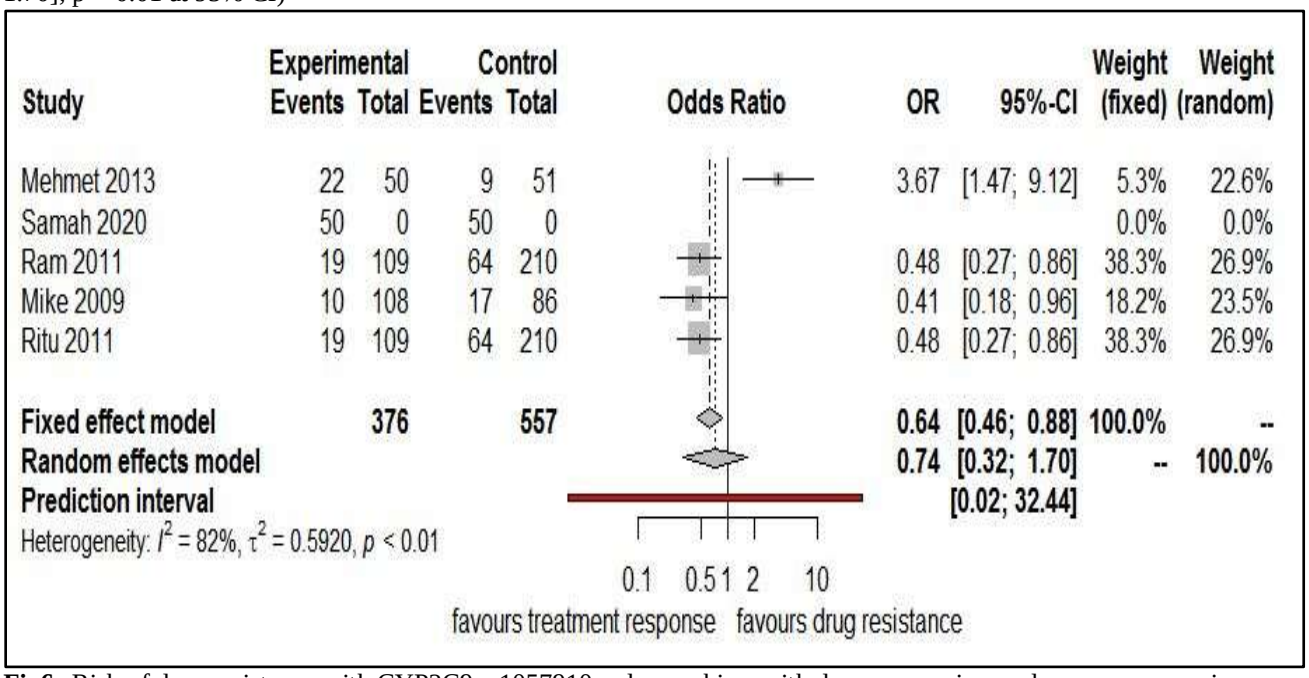

Fig6:-Risk of drug resistance with CYP2C9 rs1057910 polymorphism with drug-responsive vs drug non-responsive.

Five articles contained the data to compare the drug-responsive population (n= 282) and drug-non-responsive population (n=281) to evaluate the outcome of CYP2C19 rs4244285 polymorphism associated with treatment failure (Fig:7). A statistically significant association between CYP2C19 rs4244285genetic variation shows a higher risk of AED resistance from the data of pooled population. (OR= 0.68, [0.29-1.62], p=0.02 at 95% CI)

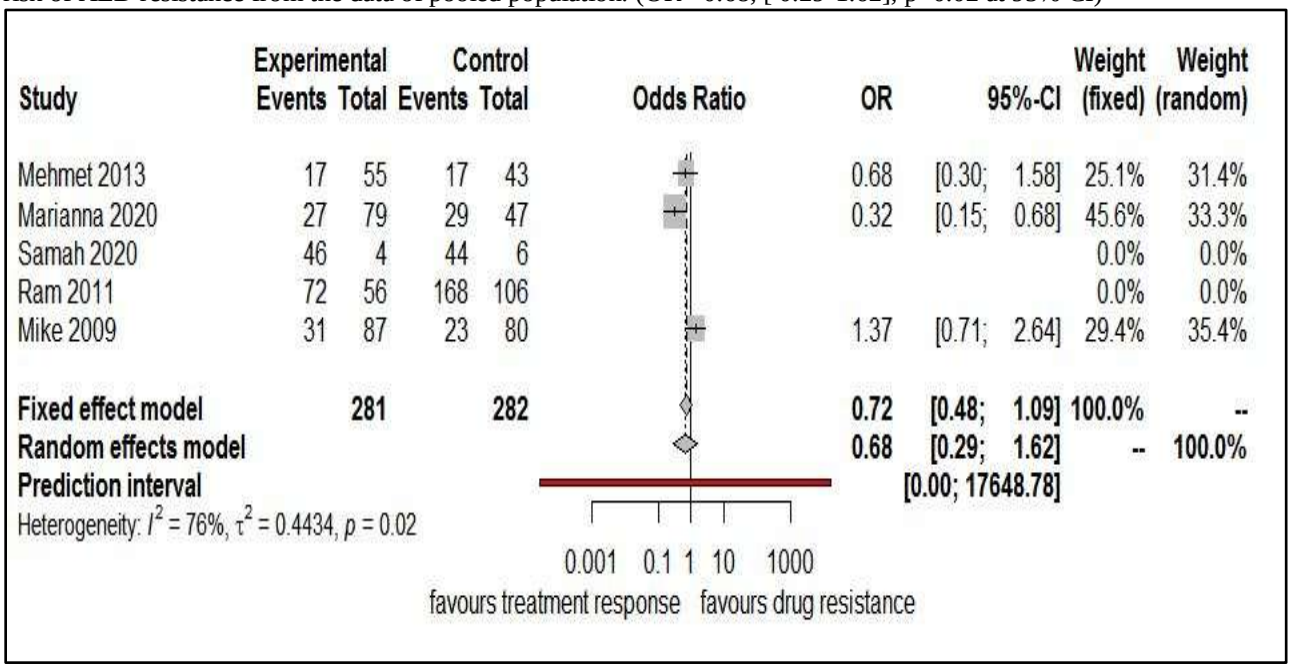

Fig7:- Risk of drug resistance with CYP2C19 rs4244285 polymorphism with drug-responsive vs drug non-responsive.

Five articles contained the data to compare the drug-responsive population (n= 764) and drug-non-responsive population (n=573) to evaluate the result of SCN2A rs2304016 polymorphism associated with treatment failure

(Fig:8). SCN2A rs2304016genetic variant shows the greater risk of AED resistance. (OR=1.20, [0.48-3.05], p=<0.01at 95% CI).

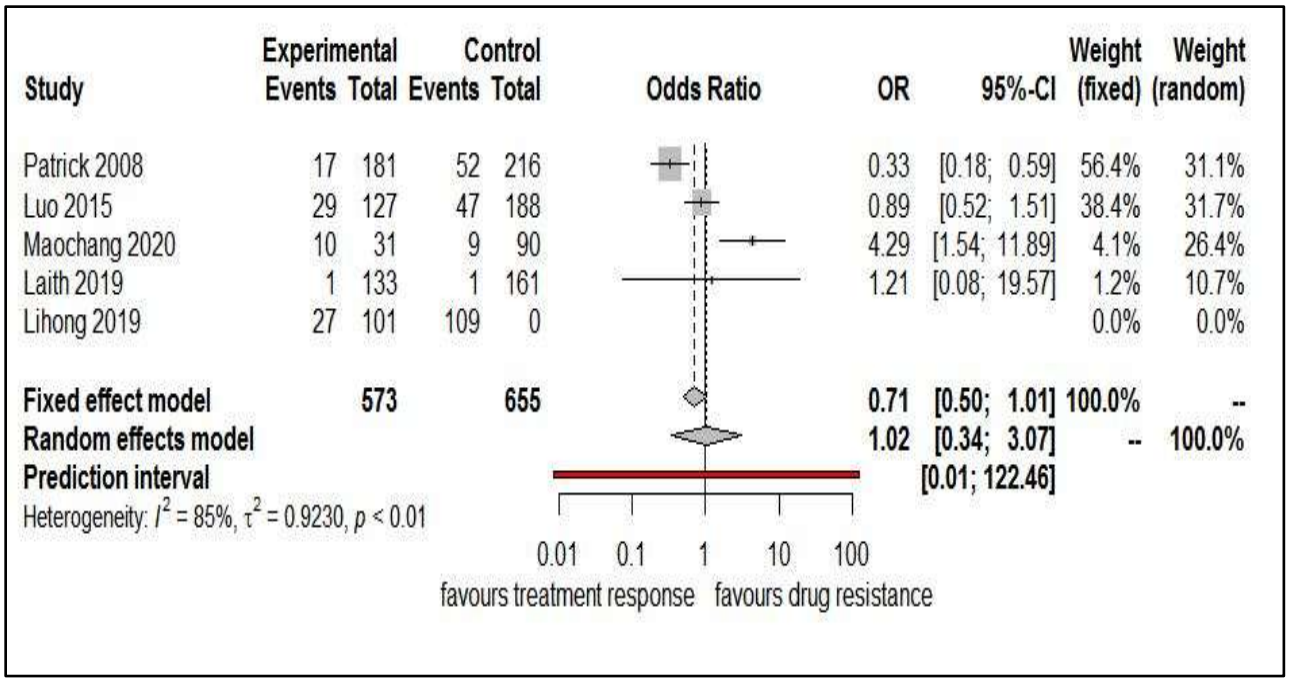

Fig8:- Risk of drug resistance with SCN2A rs2304016 polymorphism with drug-responsive vs drug non-responsive.

Six articles contained the data to compare the drug-responsive population (n= 725) and drug-non-responsive population (n=446) to assess the effect of SCN2A rs17183814 polymorphism associated with treatment failure (Fig:9). Higher risk of drug resistance was observed with SCN2A rs17183814genetic variant. (OR=1.51,[1.12-2.03], p=0.30 at 95% CI)

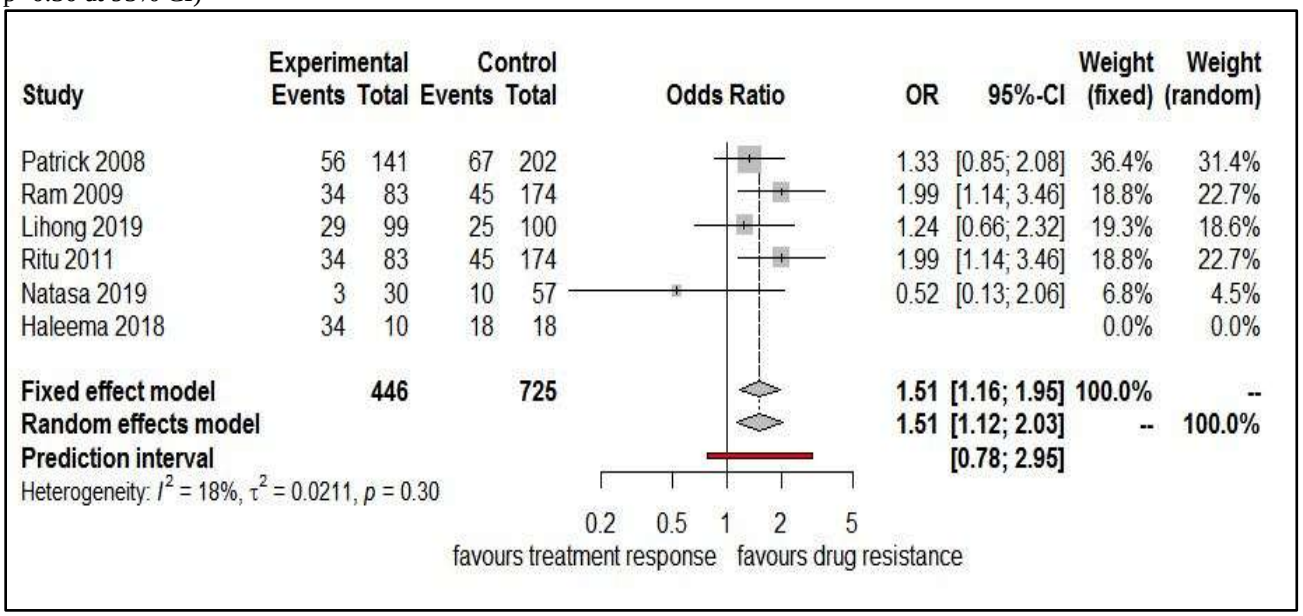

Fig9:- Risk of drug resistance with SCN2A rs17183814 polymorphism with drug-responsive vs drug non-responsive.

Assessment of publication Bias:

Funnel plots graphically summarize the extent of bias due to publication by plotting coordinates with odds ratios along the x-axis and standard error (SE) on the y-axis. Herein, we assessed publication bias in ABCC2 rs2273697 in

drug responsive vs drug non-responsive through Egger's test (Fig:10), ABCC2 rs2273697 counter enhanced funnel plot (Fig:11), ABCC2 rs3740066 in drug responsive vs drug non-responsive (Fig:12), ABCC2 rs3740066 counter enhanced funnel plot (Fig:13),ABCC2 rs717620 in drug responsive vs drug non-responsive (Fig:14),ABCC2 rs717620counter enhanced funnel plot (Fig:15), CYP2C9 rs1799853 in drug responsive vs drug non-responsive (Fig:16),CYP2C9 rs1799853counter enhanced funnel plot (Fig:17), CYP2C9 rs1057910 in drug responsive vs drug non-responsive (Fig:18),CYP2C9 rs1057910counter enhanced funnel plot (Fig:19), CYP2C19 rs4244285 in drug responsive vs drug non-responsive (Fig:20),CYP2C19 rs4244285counter enhanced funnel plot (Fig:21),SCN2A rs2304016 in drug responsive vs drug non-responsive (Fig:22),SCN2A rs2304016counter enhanced funnel plot (Fig:23), SCN2A rs17183814 in drug responsive vs drug non-responsive (Fig:24)SCN2A rs17183814counter enhanced funnel plot (Fig:25).

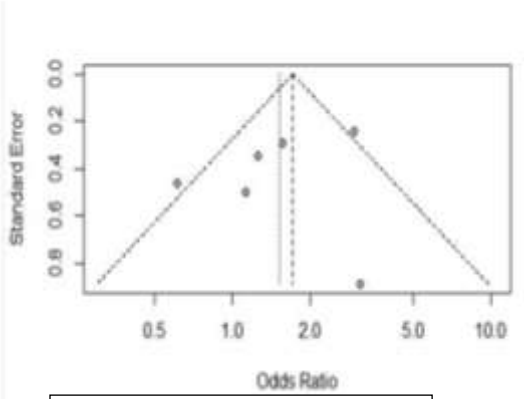

Fig:10 *ABCC2 rs2273697*

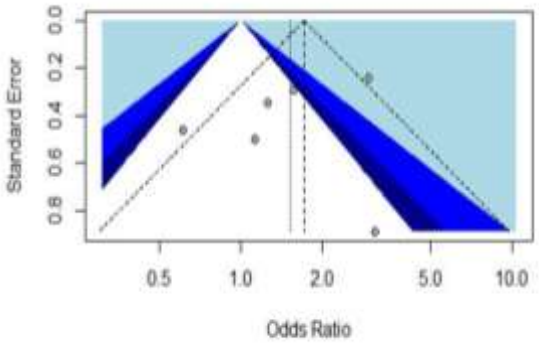

Fig:11 *ABCC2 rs2273697*

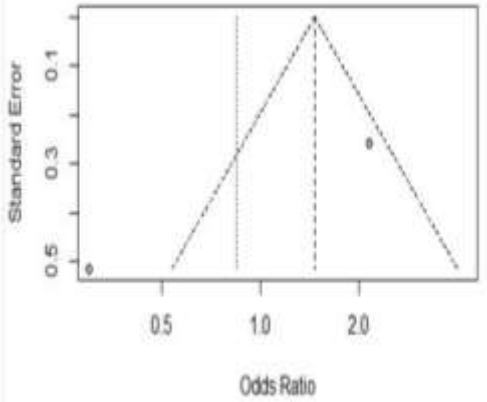

Fig:12 *ABCC2 rs3740066*

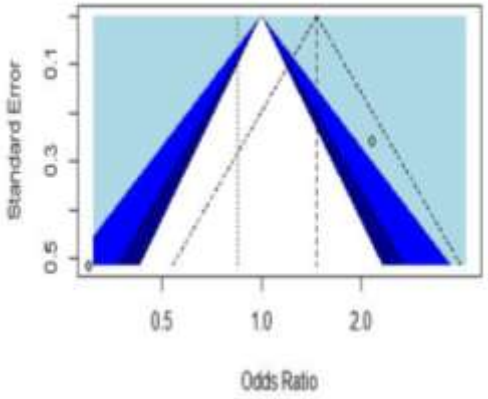

Fig:13 *ABCC2 rs3740066*

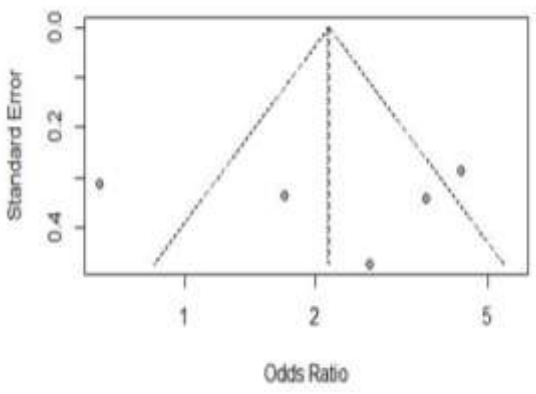

Fig:14 *ABCC2 rs717620*

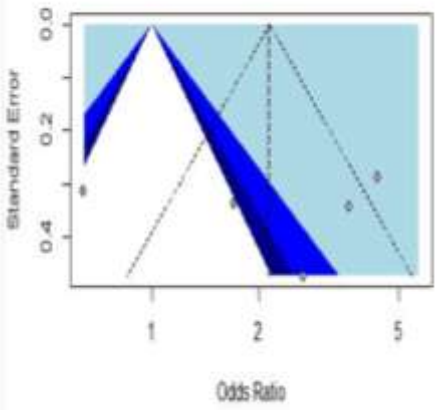

Fig:15 *ABCC2 rs717620*

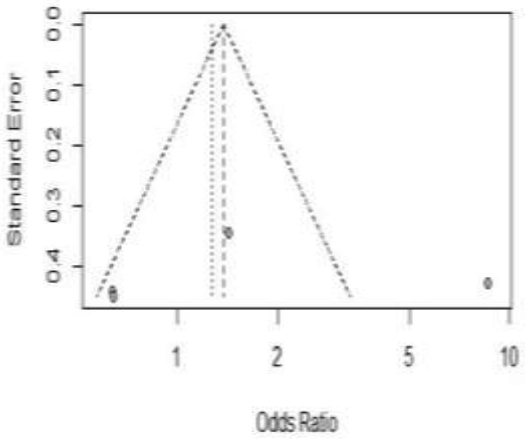

Fig:16 *CYP2C9 rs1799853*

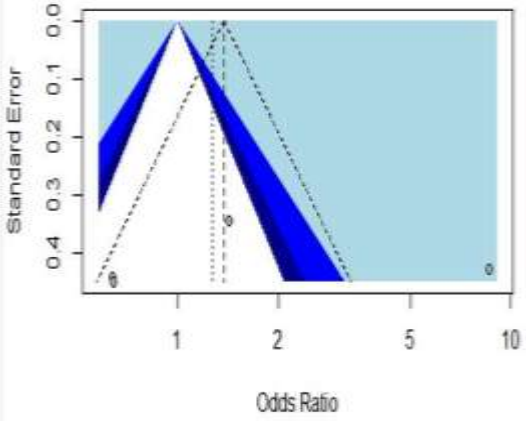

Fig:17 *CYP2C9 rs1799853*

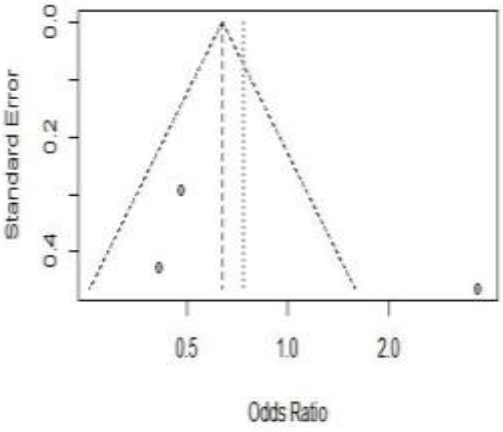

Fig:18 *CYP2C9 rs1057910*

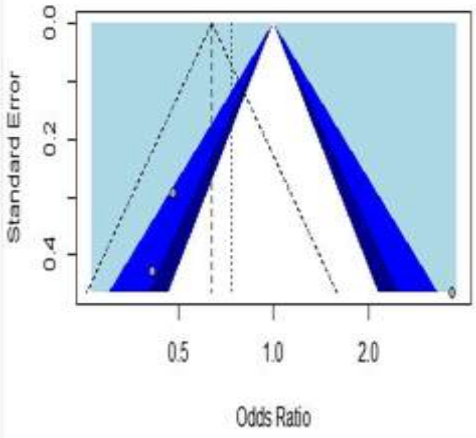

Fig:19 *CYP2C9 rs1057910*

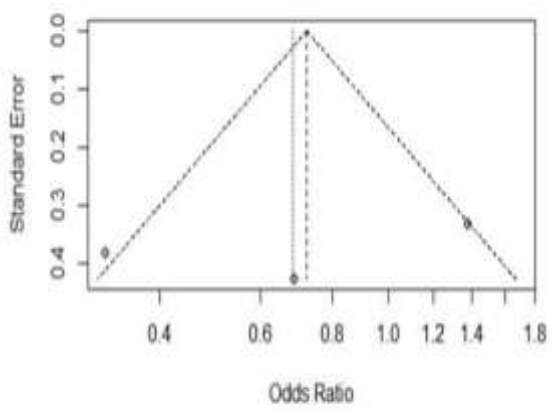

Fig:20 *CYP2C19 rs4244285*

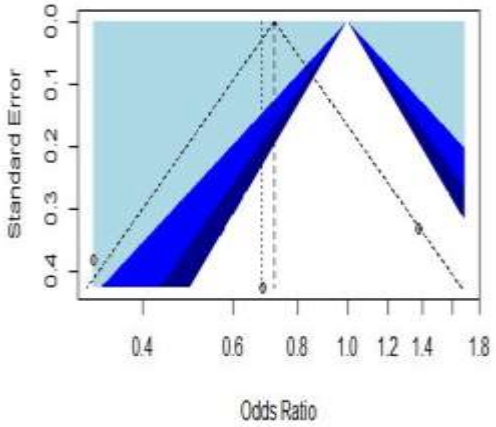

Fig:21 *CYP2C19 rs4244285*

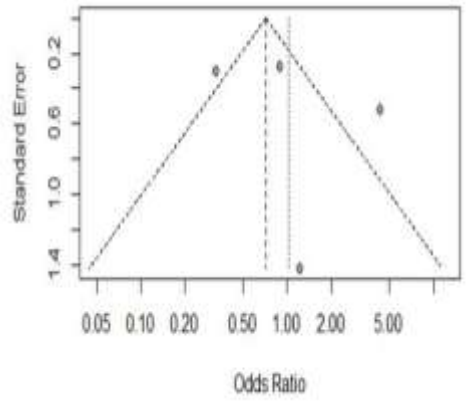

Fig:22 *SCN2A rs2304016*

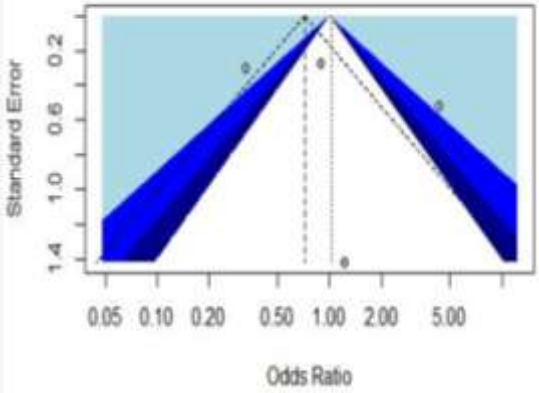

Fig:23 *SCN2A rs2304016*

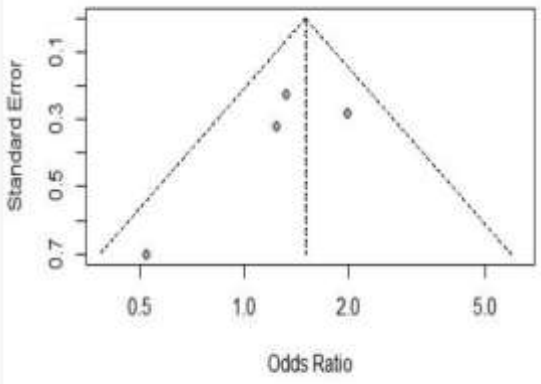

Fig:24 *SCN2A rs17183814*

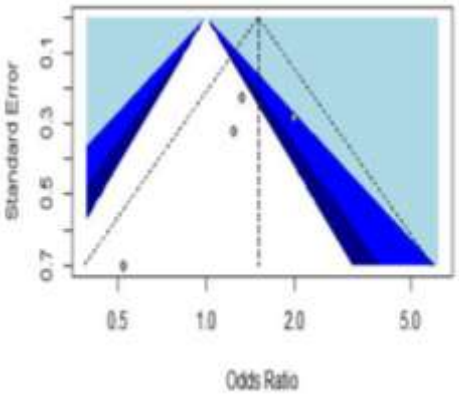

Fig:25 *SCN2A rs17183814*

To assess publication bias in meta-analysis Egger's plot is used via funnel plot. ABCC2 rs2273697 the quantifying heterogeneity value is low, ABCC2 rs 3740066 the quantifying heterogeneity value is high, ABCC2 rs 717620 the quantifying heterogeneity value is low, CYP2C9 rs 1799853the quantifying heterogeneity value is high, CYP2C9 rs

1057910the quantifying heterogeneity value is high, CYP2C19 rs 4244285the quantifying heterogeneity value is high, SCN2A rs 2304016 the quantifying heterogeneity value is low, SCN2A rs17183814 the quantifying heterogeneity value is low.

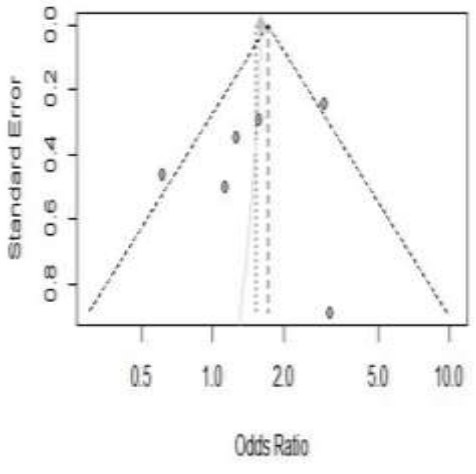

Fig:26 Egger's plot of *ABCC2 rs 2273697*

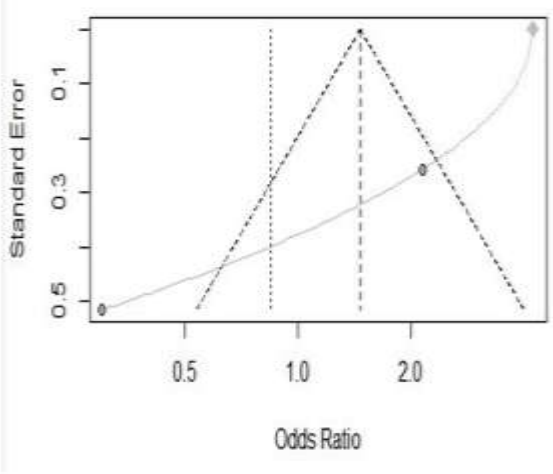

Fig:27 Egger's plot of *ABCC2 rs 3740066*

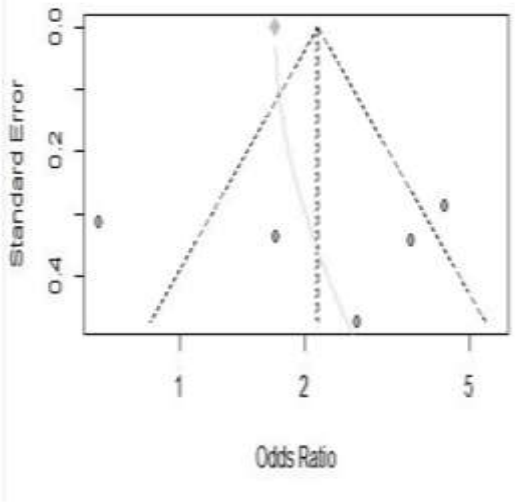

Fig:28 Egger's plot of *ABCC2 rs 717620*

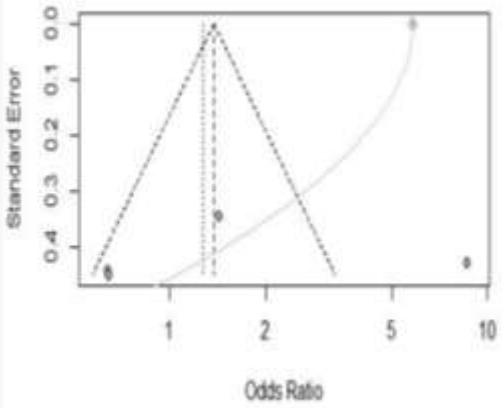

Fig:29 Egger's plot of *CYP2C9 rs 1799853*

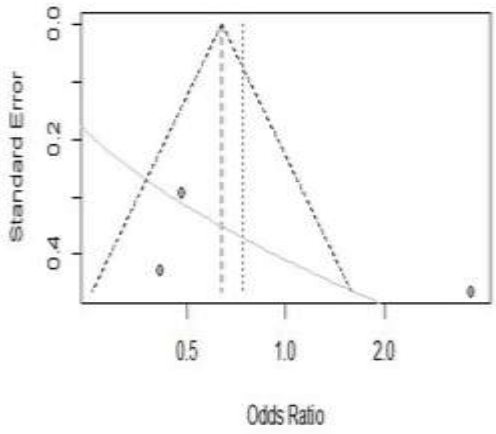

Fig:30 Egger's plot of *CYP2C9 rs 1057910*

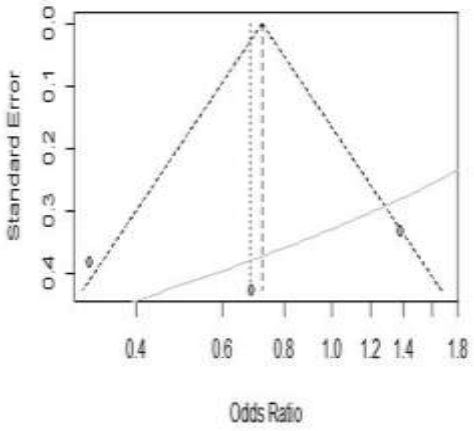

Fig:31 Egger's plot of *CYP2C19 rs 4244285*

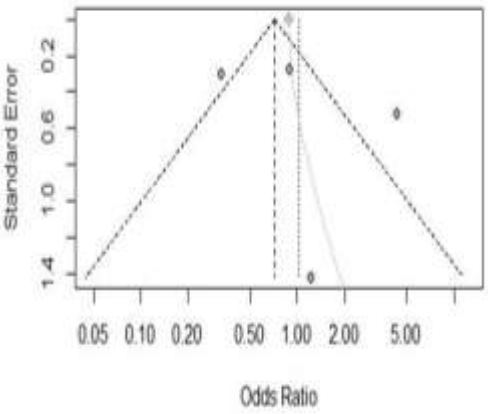

Fig:32 Egger's plot of *SCN2A rs 2304016*

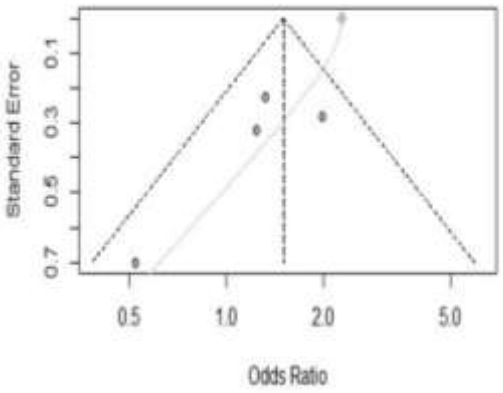

Fig:33 Egger's plot of *SCN2A rs 17183814*

Table2:- Assessment of heterogeneity.

Gene	Polymorphism	tau^2	I^2	H	Q	d.f	P value
ABCC2	rs 2273697	0.3134	68.3% [30.0%; 85.7%]	1.78 [1.20; 2.64]	18.95	6	0.0042
	rs 3740066	0	0	0	0	0	0
	rs 717620	1.1328	91.2% [84.5%; 95.0%]	3.38 [2.54; 4.49]	68.36	6	<0.0001
CYP2C9	rs 1799853	0.9610	84.4% [67.8%; 92.5%]	2.54 [1.76; 3.65]	32.15	5	<0.0001

	rs 1057910	0.5913	82.3% [54.5%; 93.1%]	2.38 [1.48; 3.82]	16.98	3	0.0007
CYP2C19	rs 4244285	1.1249	88.2% [75.1%; 94.4%]	2.91 [2.00; 4.24]	33.99	4	<0.0001
SCN2A	rs 2304016	1.3870	86.4% [72.6%; 93.3%]	2.71 [1.91; 3.85]	36.82	5	<0.0001
	rs 17183814	0.0210	18.1% [0.0%; 83.0%]	1.11 [1.00; 2.42]	4.88	4	0.2993

Discussion:-

Non-responsiveness to anti-epileptic drugs (AEDs) is a common complication associated with anti-epileptic therapy largely influenced by genetic factors, patient-specific pathological states, and environmental circumstances. Variations in genes involved in the pharmacodynamics of AEDs and their disposition such as single nucleotide polymorphisms, copy number variations, and/or restriction fragment polymorphisms can serve as predictive markers of patient response. While genetic variations in channel proteins significantly impair classical AED binding, variations in transporter can impair AED conductance across the neuronal membrane leading to AED failure[1]. Moreover, genetic variations in microsomal CYP450 enzymes can impair the bioactivation of prodrugs such as primidone and thereby decrease patient response. On the contrary, non-synonymous variations in microsomal enzymes can also lead to AED accumulation and toxicity as observed in the case of CYP2C9*2 and *3 allelic variations causing phenytoin-inducedneurotoxicity[12]. The drug transporter hypothesis is a widely held belief that multi-drug transporter failure on the blood-brain barrier (BBB) affects medication uptake in the brain, particularly AEDs[2].

Here in, we report a statistically significant association between ABCC2rs2273697 single nucleotide variation and AED (Anti-epileptic drug) resistance in epileptic adult patients. The results of our study (OR=1.51, [0.93-2.47], p=0.03 at 95% CI) are on par with previous reports published by Uferet al, (2011) that there was a reduction in Carbamazepinetransport in epileptic patients associated with ABCC2rs2273697 polymorphism (OR=2.68, [1.25-5.78], p=0.010 at 95% CI)[15], Qu et al,(2012) reported that Response to AED is affected by ABCC2 polymorphism (OR=0.915, [0.559-1.50], p=0.725 at 95% CI)[3].

Similarly, we report an association between ABCC2 rs3740066 polymorphism and AED resistance in epileptic adult and pediatric patients. The outcomes of our study (OR=0.85, [0.12-5.85], p<0.01 at 95% CI) are on par with previous results reported by Qu et al, (2012) that ABCC2 polymorphism affects AED response (OR=1.41, [0.943-2.10], p=0.094 at 95% CI)[3], Chen et al, (2018) reported that increase in VPA resistance was seen in epileptic patients with ABCC2rs3740066 polymorphism (OR=0.78, [0.36-1.69], p=0.53 at95% CI)[19].

Similarly,the association between the effect of ABCC2 rs717620 single nucleotide variations and AED resistance was reported in epileptic adult and pediatric patients. The results of our study (OR=2.13, [1.02-4.44], p<0.01 at 95% CI) are on par with previous results reported by Uferet al,(2011) that could determine the drug response in epileptic patients associated with ABCC2rs717620 polymorphism (OR=0.58, [0.25-1.37], p=0.21 at 95% CI)[15], Qu et al,(2012) reported that ABCC2 rs717620 polymorphism in epileptic patients is associated with drug resistance (OR=1.57, [1.08-2.29], p=0.018 at 95% CI)[3].

Here in, we report a statistically significant association between CYP2C9rs1799853 single nucleotide variation and AED (Anti-epileptic drug) resistance in epileptic pediatric patients. The results of our study (OR=1.27, [0.49-3.32], p<0.01 at 95% CI) are on par with previous results reported by Seven et al, (2013) that there was an increase in AED resistance associated with CYP2C9rs1799853 haplotype compared to CYP2C19 polymorphism in Turkish children (OR=0.72, [0.29-1.79], p=0.58 at 95% CI)[12], Lakhan et al,(2011) reported that CYP2C9 polymorphisms play important role in developing drug resistance in epilepsy patients (OR=0.66, [0.27-1.59], p=0.35 at 95% CI)[20].

Similarly, we report an association between the effect of CYP2C9rs1057910 single nucleotide variations and AED resistance in epileptic pediatric patients. The results of our study (OR=0.74, [0.32-1.70], p<0.01 at 95% CI) are on par with previous results reported by Seven et al, (2013) that CYP2C9rs1057910 polymorphism had an increased frequency of drug resistance in Turkish children (OR=1.91, [0.68-5.46], p=0.26 at 95% CI)[12], Lakhan et al, (2011) reported that CYP2C9 polymorphisms play a significant role in epilepsy treatment response (OR=0.57, [0.32-1.00], p=0.05 at 95% CI)[20].

Here in, we report a statistically significant association between CYP2C19rs4244285 single nucleotide variation and AED (Anti-epileptic drug) resistance in epileptic pediatric patients. The results of our study (OR=0.68, [0.29-1.62], p=0.02 at 95% CI) are on par with previous results reported by Lakhan et al, (2011) was that in the monomorphic north Indian population, there was no significant difference in allele or genotypes of CYP2C19rs4244285 (OR=0.93, [0.68-1.27], p=1.27 at 95% CI)[20], Makowskaet al,(2010) reported that in children presence of drug resistance epilepsy could be associated with CYP2C19 polymorphism(OR=0.55, [0.3-1.05], p=0.07 at 95% CI)[16].

Here in, we report a statistically significant association between SCN2Ars2304016 single nucleotide variation and AED (Anti-epileptic drug) resistance in epileptic adult patients. The results of our study (OR=1.20, [0.48-3.05], p<0.01 at 95% CI) are on par with previous results reported by Zhou et al, (2015) that drug resistance in epilepsy may not be associated with SCN2A polymorphism (OR=0.988, [0.569-1.715], p=0.965 at 95% CI)[21], Liu et al,(2020) reported that in Chinese epileptic patients, therapeutic responsiveness to VPA monotherapy was associated with SCN2A rs2304016 polymorphism (OR=3.18, [1.10-9.14], p=0.041 at 95% CI)[22].

Similarly,the association between the effect of SCN2A rs17183814 polymorphism and AED resistance was reported in epileptic adult patients. The outcome of our study (OR=1.51, [1.12-2.03], p=0.30 at 95% CI) are on par with previous results reported by Kumari et al, (2011) is thathigher frequency of drug resistance in epileptic patients associated with SCN2A rs17183814 polymorphism (OR=1.44, [0.84-2.48], p=0.97 at 95% CI)[23], Pejanovic-Skobicet al, (2019) reported that there was no significant impact of SCN2Ars17183814 polymorphism on Lamotrigine efficacy in Herzegovina population (OR=0.609, [0.180-2.065], p=0.570 at 95% CI)[24].

Conclusion:-

The risk of the global prevalence of AED treatment resistance is 30-40% which warrants the risk of treatment failure and predisposes the risk of patient mortality and or compromises the quality of treatment.Herein we have identified genetic variants as a predisposing factor for AED treatment failure. It is likewise diagnosed that genetic factors affect the response and effectiveness of anti-epileptic drugs (AEDs).Herein, we reported a significant association between SNV and the rise of drug resistance in ABCC2, CYP2C9, CYP2C19 & SCN2A genes.Here patients who are at high risk of developing recurrent seizures should be screened for genetic variations stated above.Such genetic screening can serve as prognostic markers of treatment response which can maximize the quality of epilepsy pharmacotherapy with AEDs, decrease the probability of adverse events, and minimize healthcare costs.

Limitations:

The limitations in the findings of this study could be addressed as follows

Owing to the high heterogeneity in outcome between the related articles, random effects models were used to test association .considering the residual variability with random effects models which are often unexplained the reliability of results obtained is questionable, hence more studies with less heterogeneity are to be included to do fixed effects plots.

Future Objectives:

In this study, the effect of variations in ABCC2, CYP2C9, CYP2C19, & SCN2A genes on treatment response to anti-convulsantswas assessed, and found that there will be a development of drug resistance which causes recurrence of seizure episodes. According to the International League Against Epilepsy (ILAE) epilepsy is defined as a brain illness characterized by at the minimum of two unprovoked seizures occurring within 24 hours of each other.According to the World Health Organization, epilepsy is one of the most frequent neurological illnesses (WHO), with over 50 million individuals suffering from it globally.Conducting such a study is important as,It affects people of all ages and has a significant impact on the morbidity and mortality of those who suffer from it.Although the cause of epilepsy is unknown, special evidence suggests that epilepsy is due to genetic variations.Anti-epileptic drug (AED) nonresponsiveness is a prevalent problem inepilepsy treatment.It is likewise diagnosed that genetic factors have an effect on the response and effectiveness of anti-epileptic drugs

(AEDs).Herein, we reported a significant association between SNV and the rise of drug resistance in ABCC2, CYP2C9, CYP2C19 & SCN2A genes.Here subjects who are at high possibility of developing recurrent seizures should be screened for the genetic variations stated above.Such genetic screening can serve as prognostic markers of treatment response which in turn can rise the quality of epilepsy pharmacotherapy with AEDs, decrease the risk of adverse events, and minimize healthcare costs.

Reference:-

1. Leandro, K., Bicker, J., Alves, G., Falcão, A., & Fortuna, A. (2019). ABC transporters in drug-resistant epilepsy: mechanisms of up-regulation and therapeutic approaches. Pharmacologicalresearch, 144, 357–376. https://doi.org/10.1016/j.phrs.2019.04.031.
2. Sporis, D., Bozina, N., Basić, S., Lovrić, M., Babić, T., Susak, I., &Marković, I. (2013). Lack of association between polymorphism in ABCC2 gene and response to antiepileptic drug treatment in Croatian patients with epilepsy. Collegium antropologicum, 37(1), 41–45.
3. Qu, J., Zhou, B. T., Yin, J. Y., Xu, X. J., Zhao, Y. C., Lei, G. H., Tang, Q., Zhou, H. H., & Liu, Z. Q. (2012). ABCC2 polymorphisms and haplotypes are associated with drug resistance in Chinese epileptic patients. CNS neuroscience &therapeutics,18(8), 647–651. https://doi.org/10.1111/j.1755-5949.2012.00336.
4. Al-Eitan, L. N., Al-Dalala, I. M., Elshammari, A. K., Khreisat, W. H., Nimiri, A. F., Alnaamneh, A. H., Aljamal, H. A., & Alghamdi, M. A. (2020). Genetic Association of Epilepsy and Anti-Epileptic Drugs Treatment in Jordanian Patients. Pharmacogenomics and personalized medicine, 13, 503–510. https://doi.org/10.2147/PGPM.S273125.
5. Chen, J., Su, Q., Qin, J., Zhou, Y., Ruan, H., Chen, Z., Chen, Z., Li, H., Zhou, Y., Zhou, S., Wang, X., Zhou, L., & Huang, M. (2019). Correlation of MCT1 and ABCC2 gene polymorphisms with valproic acid resistance in patients with epilepsy on valproic acid monotherapy. Drug metabolism and pharmacokinetics, 34(3), 165–171. https://doi.org/10.1016/j.dmpk.2018.01.006.
6. Sha'ari, H. M., Hadrian, B. S., Baum, L., Saruwatari, J., Tan, H. J., Rafia, M. H., Raymond, A. A., Kwan, P., Ishitsu, T., Nakagawa, K., Lim, K. S., & Mohamed, Z. (2014). ABCC2 rs2273697 and rs3740066 polymorphisms and resistance to antiepileptic drugs in Asia Pacific epilepsy cohorts. Pharmacogenomics, 15(4), 459–466. https://doi.org/10.2217/pgs.13.239.
7. Grover, S., &Kukreti, R. (2013). A systematic review and meta-analysis of the role of ABCC2 variants on drug response in patients with epilepsy. Epilepsia, 54(5), 936–945. https://doi.org/10.1111/epi.12132.
8. Chen, P., Yan, Q., Xu, H., Lu, A., & Zhao, P. (2014). The effects of ABCC2 G1249A polymorphism on the risk of resistance to antiepileptic drugs: a meta-analysis of the literature. Genetic testing and molecular biomarkers, 18(2), 106–111. https://doi.org/10.1089/gtmb.2013.0362.
9. Qian, L., Fang, S., Yan, Y. L., Zeng, S. S., Xu, Z. J., & Gong, Z. C. (2017). The ABCC2 c.-24C>T polymorphism increases the risk of resistance to antiepileptic drugs: A meta-analysis. Journal of clinical neuroscience: official journal of the Neurosurgical Society of Australasia, 37, 6–14. https://doi.org/10.1016/j.jocn.2016.10.014.
10. Kwan, P., Wong, V., Ng, P. W., Lui, C. H., Sin, N. C., Wong, K. S., & Baum, L. (2011). Gene-wide tagging study of the association between ABCC2, ABCC5, and ABCG2 genetic polymorphisms and multidrug resistance in epilepsy. Pharmacogenomics, 12(3), 319–325. https://doi.org/10.2217/pgs.10.183.
11. Li, X., Zhang, J., Wu, X., Yan, H., Zhang, Y., He, R. H., Tang, Y. J., He, Y. J., Tan, D., Mao, X. Y., Yin, J. Y., Liu, Z. Q., Zhou, H. H., & Liu, J. (2016). Polymorphisms of ABAT, SCN2A, and ALDH5A1 may affect valproic acid responses in the treatment of epilepsy in Chinese. Pharmacogenomics, 17(18), 2007–2014. https://doi.org/10.2217/pgs-2016-0093.
12. Seven, M., Batar, B., Unal, S., Yesil, G., Yuksel, A., &Guven, M. (2014). The effect of genetic polymorphisms of cytochrome P450 CYP2C9, CYP2C19, and CYP2D6 on drug-resistant epilepsy in Turkish children. Molecular diagnosis & therapy, 18(2), 229–236. https://doi.org/10.1007/s40291-013-0078-8.
13. Nazish, H. R., Ali, N., & Ullah, S. (2018). The possible effect of SCN1A and SCN2A genetic variants on carbamazepine response among Khyber Pakhtunkhwaepileptic patients, Pakistan. Therapeutics and clinical risk management, 14, 2305–2313. https://doi.org/10.2147/TCRM.S180827.
14. Ufer, M., Mosyagin, I., Muhle, H., Jacobsen, T., Haenisch, S., Häsler, R., Faltraco, F., Remmler, C., von Spiczak, S., Kroemer, H. K., Runge, U., Boor, R., Stephani, U., &Cascorbi, I. (2009). Non-response to antiepileptic pharmacotherapy is associated with the ABCC2 -24C>T polymorphism in young and adult patients with epilepsy. Pharmacogenetics and genomics, 19(5), 353–362. https://doi.org/10.1097/fpc.0b013e328329940b.

15. Ufer, M., von Stülpnagel, C., Muhle, H., Haenisch, S., Remmler, C., Majed, A., Plischke, H., Stephani, U., Kluger, G., &Cascorbi, I. (2011). Impact of ABCC2 genotype on antiepileptic drug response in Caucasian patients with childhood epilepsy. Pharmacogenetics and genomics, 21(10), 624–630. https://doi.org/10.1097/FPC.0b013e3283498131.
16. Makowska, M., Smolarz, B., Bryś, M., Forma, E., &Romanowicz, H. (2020). An association between the rs1799853 and rs1057910 polymorphisms of CYP2C9, the rs4244285 polymorphism of CYP2C19, and the prevalence rates of drug-resistant epilepsy in children. The International journal of neuroscience, 1–8. Advanced online publication. https://doi.org/10.1080/00207454.2020.178111.
17. Guo, Y., Hu, C., He, X., Qiu, F., & Zhao, L. (2012). Effects of UGT1A6, UGT2B7, and CYP2C9 genotypes on plasma concentrations of valproic acid in Chinese children with epilepsy. Drug metabolism and pharmacokinetics, 27(5), 536–542. https://doi.org/10.2133/dmpk.dmpk-11-nt-144.
18. Chatzistefanidis, D., Lazaros, L., Giaka, K., Nakou, I., Tzoufi, M., Georgiou, I., Kyritsis, A., &Markoula, S. (2016). UGT1A6- and UGT2B7-related valproic acid pharmacogenomics according to age groups and total drug concentration levels. Pharmacogenomics, 17(8), 827–835. https://doi.org/10.2217/pgs-2016-0014.
19. Chen, J., Su, Q. B., Tao, Y. Q., Qin, J. M., Zhou, Y., Zhou, S., Li, H. L., Chen, Z. J., Zhou, Y. F., Zhou, L. M., Wang, X. D., & Huang, M. (2018). ABCC2 rs2273697 is associated with valproic acid concentrations in patients with epilepsy on valproic acid monotherapy. Die Pharmazie, 73(5), 279–282. https://doi.org/10.1691/ph.2018.7344.
20. Lakhan, R., Kumari, R., Singh, K., Kalita, J., Misra, U. K., & Mittal, B. (2011). Possible role of CYP2C9 & CYP2C19 single nucleotide polymorphisms in drug-refractory epilepsy. The Indian journal of medical research, 134(3), 295–301.
21. Zhou, L., Cao, Y., Long, H., Long, L., Xu, L., Liu, Z., Zhang, Y., & Xiao, B. (2015). ABCB1, ABCC2, SCN1A, SCN2A, GABRA1 gene polymorphisms and drug-resistant epilepsy in the Chinese Han population. Die Pharmazie, 70(6), 416–420.
22. Liu, M., Mao, J., Xu, H., Wang, J., Zhao, P., Xu, Q., & Du, Z. (2020). Effects of SCN1A and SCN2A polymorphisms on responsiveness to valproic acid monotherapy in epileptic children. Epilepsy research, 168, 106485. https://doi.org/10.1016/j.eplepsyres.2020.106485.
23. Kumari, R., Lakhan, R., Garg, R. K., Kalita, J., Misra, U. K., & Mittal, B. (2011).Pharmacogenomic association study on the role of drug-metabolizing, drug transporters, and drug target gene polymorphisms in drug-resistant epilepsy in a north Indian population. Indian journal of human genetics, 17 Suppl 1(Suppl 1), S32–S40. https://doi.org/10.4103/0971-6866.80357.
24. Pejanovic-Skobic, N., Markovic, I., Bozina, N., & Basic, S. (2019). Lack of association of SCN2A rs17183814 polymorphism with the efficacy of lamotrigine monotherapy in patients with focal epilepsy from Herzegovina area, Bosnia and Herzegovina. Epilepsy research, 158, 106221. https://doi.org/10.1016/j.eplepsyres.2019.106221.
25. Grover, S., Gourie-Devi, M., Bala, K., Sharma, S., &Kukreti, R. (2012). Genetic association analysis of transporters identifies ABCC2 loci for seizure control in women with epilepsy on first-line antiepileptic drugs. Pharmacogenetics and genomics, 22(6), 447–465. https://doi.org/10.1097/FPC.0b013e3283528217.
26. Hung, C. C., Ho, J. L., Chang, W. L., Tai, J. J., Hsieh, T. J., Hsieh, Y. W., &Liou, H. H. (2011). Association of genetic variants in six candidate genes with valproic acid therapy optimization Pharmacogenomics, 12(8), 1107–1117. https://doi.org/10.2217/pgs.11.64
27. Khreisat, W. H., &Aljamal, H. A. (2019). Effects of MTHFR and ABCC2 gene polymorphisms on antiepileptic drug responsiveness in Jordanian epileptic patients. Pharmacogenomics and personalized medicine, 12, 87–95. https://doi.org/10.2147/PGPM.S211490.
28. Al-Eitan, L. N., Al-Dalalah, I. M., &Aljamal, H. A. (2019). Effects of GRM4, SCN2A and SCN3B polymorphisms on antiepileptic drugs responsiveness andepilepsy susceptibility. Saudi pharmaceutical journal: SPJ: the official publicationof the Saudi Pharmaceutical Society, 27(5), 731–737. https://doi.org/10.1016/j.jsps.2019.04.009.
29. Hadrian, 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. https://doi.org/10.2217/pgs.13.104.
30. 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. British journal of clinical pharmacology, 68(2), 214–220. https://doi.org/10.1111/j.1365-2125.2009.03437.x.

31. Shi, L., Zhu, M., Li, H., Wen, Z., Chen, X., Luo, J., Lin, C., & Zhang, Z. (2019).SCN1A and SCN2A polymorphisms are associated with response to valproic acid inChinese epilepsy patients. European journal of clinical pharmacology, 75(5), 655–663. https://doi.org/10.1007/s00228-019-02633-0.
32. Kwan, P., Poon, W. S., Ng, H. K., Kang, D. E., Wong, V., Ng, P. W.,Lui, C. H.,Sin, N. C., Wong, K. S., & Baum, L. (2008). Multidrug resistance in epilepsy and polymorphisms in the voltage-gated sodium channel genes SCN1A, SCN2A, and SCN3A: correlation among phenotype, genotype, and mRNA expression. Pharmacogenetics andgenomics, 18(11), 989–998. https://doi.org/10.1097/FPC.0b013e3283117d67.
33. Eltalal, S., El Ayouty, M., El-Said, A., & Wahba, Y. (2020). CYP2C9 (*2&*3) and CYP2C19 (*2&*3) polymorphisms among children with nonlesional epilepsy: a single-center study. Acta neurologicaBelgica, 10.1007/s13760-020-01442-y. Advanced online publication. https://doi.org/10.1007/s13760-020-01442-y.
34. López-García, M. A., Feria-Romero, I. A., Serrano, H., Rayo-Mares, D., Fagiolino, P., Vázquez, M., Escamilla-Núñez, C., Grijalva, I., Escalante-Santiago, D., & Orozco-Suarez, S. (2017). Influence of genetic variants of CYP2D6, CYP2C9, CYP2C19, and CYP3A4 on antiepileptic drug metabolism in pediatric patients with refractory epilepsy. Pharmacological reports: PR, 69(3), 504–511. https://doi.org/10.1016/j.pharep.2017.01.007.
35. Silvado, C. E., Terra, V. C., &Twardowschy, C. A. (2018). CYP2C9 polymorphisms in epilepsy: influence on phenytoin treatment. Pharmacogenomics and personalized medicine, 11, 51–58. https://doi.org/10.2147/PGPM.S108113.
36. Inoue, K., Suzuki, E., Yazawa, R., Yamamoto, Y., Takahashi, T., Takahashi, Y., Imai, K., Koyama, S., Inoue, Y., Tsuji, D., Hayashi, H., & Itoh, K. (2014). Influence of uridine diphosphate glucuronosyltransferase 2B7 -161C>T polymorphism on the concentration of valproic acid in pediatric epilepsy patients. Therapeutic drug monitoring, 36(3), 406–409. https://doi.org/10.1097/FTD.0000000000000012.
37. Zhang, H., Zhang, W., Li, Y., Yan, J., Zhang, J., & Wang, B. (2018). Correlationsbetween UGT2B7∗2 gene polymorphisms and plasma concentrations of carbamazepine and valproic acid in epilepsy patients. Brain & development, 40(2), 100–106. https://doi.org/10.1016/j.braindev.2017.09.004
38. Du, Z., Jiao, Y., & Shi, L. (2016). Association of UGT2B7 and UGT1A4 Polymorphisms with Serum Concentration of Antiepileptic Drugs in Children. Medical science monitor: international medical journal of experimental and clinical research, 22, 4107–4113. https://doi.org/10.12659/msm.897626.
39. Chu, X. M., Zhang, L. F., Wang, G. J., Zhang, S. N., Zhou, J. H., & Hao, H. P. (2012). Influence of UDP-glucuronosyltransferase polymorphisms on valproic acid pharmacokinetics in Chinese epilepsy patients. European journal of clinical pharmacology, 68(10), 1395–1401. https://doi.org/10.1007/s00228-012-1277-7.
40. Shen, C., Zhang, B., Liu, Z., Tang, Y., Zhang, Y., Wang, S., Guo, Y., Ding, Y., Wang, S., & Ding, M. (2017). Effects of ABCB1, ABCC2, UGT2B7 and HNF4α genetic polymorphisms on oxcarbazepine concentrations and therapeutic efficacy in patients with epilepsy. Seizure, 51, 102–106. https://doi.org/10.1016/j.seizure.2017.07.015.
41. Wang, Q., Zhao, L., Liang, M., Dong, Y., Yun, W., Qiu, F., Meng, H., & Guo, Y.(2016). Effects of UGT2B7 Genetic Polymorphisms on Serum Concentrations of Valproic Acid in Chinese ChildrenWith Epilepsy ComedicatedWithLamotrigine. Therapeutic drug monitoring, 38(3), 343–349.https://doi.org/10.1097/FTD.0000000000000271.
42. Sun, Y. X., Zhuo, W. Y., Lin, H., Peng, Z. K., Wang, H. M., Huang, H. W., Luo, Y. H., & Tang, F. Q. (2015). The influence of UGT2B7 genotype on valproic acid pharmacokinetics in Chinese epilepsy patients. Epilepsy research, 114, 78–80. https://doi.org/10.1016/j.eplepsyres.2015.04.015.