Abstract. Epilepsy is a common, serious neurological disorder worldwide. Although this disease can be successfully treated in most cases, not all patients respond favorably to medical treatments, which can lead to pharmacoresistant epilepsy. Drug-resistant epilepsy can be caused by a number of mechanisms that may involve environmental and genetic factors, as well as disease- and drug-related factors. In recent years, numerous studies have demonstrated that genetic variation is involved in the drug resistance of epilepsy, especially genetic variations found in drug resistance-related genes, including the voltage-dependent sodium and potassium channels genes, and the metabolizer of endogenous and xenobiotic substances genes. The present review aimed to highlight the genetic variants that are involved in the regulation of drug resistance in epilepsy; a comprehensive understanding of the role of genetic variation in drug resistance will help us develop improved strategies to regulate drug resistance efficiently and determine the pathophysiological processes that underlie this common human neurological disease.

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1. Introduction

Epilepsy is one of the most common neurological diseases worldwide and is considered a major public health problem (1,2). The International League Against Epilepsy (ILAE) has established that the term ‘epilepsy’ refers to a disease of the brain that meets any of the following conditions: i) At least two non-induced seizures, or reflexes, that occur ≥24 h apart; ii) one non-induced seizure, or reflex, and a risk of further seizures similar to the general recurrence risk (≥60%) following two non-induced seizures that occur over the next 10 years; or iii) the diagnosis of an epilepsy syndrome (3,4). Epilepsy is considered to be resolved when an individual with epilepsy has remained seizure-free for 10 years and without antiepileptic drug treatment for ≥5 years (4).

For the most accurate study of epilepsy, the ILAE (5,6) has organized and classified seizures and several epilepsy types as focal, generalized and of unknown onset, based on certain characteristics, including seizure type, electroencephalography (EEG) features, imaging studies, age-related features and
triggering factors, such as comorbidities and prognosis (6,7); this classification involved the work of epileptologists, neurophysiologists and epilepsy researchers (6).

A previous study demonstrated that epileptic seizures are associated with several mechanisms that involve the glutamate excitotoxicity process, microglial activation, mitochondrial dysfunction, degenerative processes, and the presence of reactive oxygen species and oxidative stress (8). In addition, it has previously been reported that certain regulatory processes are involved at the transcriptional level; for example, the nuclear transcription factor erythroid-derived-2-like 2 was revealed to serve a role in epileptic seizures (9,10). A recent study conducted by our group used microarray analysis in children with epilepsy to demonstrate that those with epilepsy overexpressed genes that were related to the transcriptional factor cAMP-response element binding protein (CREB) compared with normal children, in addition to significantly altered expression levels of genes involved in energy metabolism, redox balance and the immune response (11). The differential gene expression, particularly genes related to CREB, observed in children before and after the administration of valproic acid indicated that the activity of antiepileptic drugs (AED) is dependent on target genes. These data suggested a role for genetics in epilepsy development and highlighted the importance of studying the genetic mechanisms associated with drug resistance. This would provide an improved understanding of the impact of pharmacological treatment on epilepsy and in the patient's daily activities, of which both are influenced by: i) The patient's response to treatment; ii) the relationship between the number and type of seizures, and the modified transportation of proteins or their receptors due to the drug's activity and the presence of genetic variations; iii) the possible influence of the phenotypic characteristics of the patient in response to the treatment; iv) the impact of the presence of the genetic variants in the functionality of the transporting proteins and AED target proteins; v) the interference of the potential alterations in the target protein on the mechanism of action of the AED due to the presence of the variant; vi) the influence of the inflammatory and immunological response; vii) the predisposition to some of the different aspects of epilepsy, including refractoriness or decreased sensitivity to the AED effect; and viii) the result following the combination of several of these or other mechanisms (12-15). In accordance with the last point, the objective of the present review was to focus on describing the findings of genetic alterations involved in pharmacoresistant epilepsy.

2. Pharmacoresistant epilepsy

The term pharmacoresistant epilepsy refers to a type of epilepsy that does not respond to at least two AEDs, which were chosen and used in monotherapy or combination therapy (bi- or polytherapy) and fail to fully control seizures for an adequate period (16). In 2011, the ILAE proposed to standardize the definition of pharmacoresistant epilepsy as the presence of seizures in a period of 6 months, even under proper therapeutic regimens (either monotherapy or in combination) (16). Two studies performed in 2000 and 2012 reported that people with epilepsy (PWE) responded differently to AED treatment, since 47-49.5% of the patients required one AED to control the seizures, 13-13.3% required a second AED, and 3.7-4% needed a third AED, which was administered either alone or in combination (17,18). To summarize, Kwan and Brodie (17) observed that in a prospective study of 525 PWE (age, 9-93 years), 333 of them (63%) remained seizure-free during AED administration and seizures that did occur were more persistent in patients with symptomatic and cryptogenic epilepsy (40%) compared with those with idiopathic epilepsy (26%). Moreover, among 470 previously untreated patients, 222 of them (47%) became seizure-free during treatment with their first AED, 67 patients (14%) became seizure-free during treatment with a second or third AED and 12 patients (3%) were controlled with two AEDs administered together (17). Brodie et al (18) subsequently discovered that patients have differential responses to AEDs; out of 1,098 PWE (ages, 9-93 years) studied, 749 of them (68%) were seizure-free with AED monotherapy, but in 272 patients (25%), freedom from seizures was never attained. Moreover, <2% of patients became seizure-free with the use of up to six or seven AEDs (18). In addition to the above findings, epidemiological studies conducted among children and adults have discovered that 20-40% of PWE present with pharmacoresistant epilepsy (19-22), which negatively impacts their quality of life because it is also associated with increases in psychiatric comorbidities and the risk of premature death and social discrimination (23).

It is important to highlight that pharmacoresistant epilepsy may also cause serious socioeconomic problems. For instance, Argumosa and Herranz (24) evaluated the economic cost of controlled and uncontrolled epilepsy in Spain (participants were <14 years old) and reported that the mean annual cost of controlled epilepsy was $2,002.36 USD, whereas the cost of uncontrolled epilepsy was $5,348.50 USD; thus, uncontrolled epilepsy was 2.7 times more expensive compared with controlled epilepsy. Given the elevated costs of treatment, alternative therapeutic approaches, such as the ketogenic diet (25), high doses of steroids (26) and brain surgery (27) have all been implemented. The ketogenic diet has proved beneficial in PWE in which pharmacological and/or surgical treatment is not effective; this diet is centered around a very high-fat and low-carbohydrate intake, reducing carbohydrates to <10% of used energy (90% of the total caloric intake comes from fat, 6% from protein and 4% from carbohydrates). These proportions trigger a systemic shift from glucose metabolism towards the metabolism of fatty acids, which yields ketone bodies that serve as the energy source to replace glucose in the brain (28). In patients with pharmacoresistant epilepsy, a ketogenic diet has been observed to improve the quality of life and decreases seizure frequency in ~30% of patients (25). In a significant number of patients with pharmacoresistant epilepsy, curative epilepsy surgery cannot be offered since there are multiple epileptogenic zones; for these patients, neurostimulation techniques, such as vagus nerve stimulation, deep brain stimulation and responsive neurostimulation, are viable treatment options that should be considered in every patient with this type of epilepsy that is unsuitable for surgery (27,29). These techniques provide palliative care, resulting in a 10-80% reduction in seizure occurrence (29). Furthermore, if all the aforementioned treatment approaches fail to control the seizures, cannabidiol (Epidiolex®) can be prescribed; this is a pharmaceutical product approved by the U.S. Food and Drug Administration that consists of 99% cannabidiol derived...
from cannabis (30,31). A previous study reported that out of 43 Mexican children with pharmacoresistant epilepsy, a decrease in the number of epileptic seizures were observed in 81.3% of patients and 20.9% patients displayed a reduction in the number of AEDs with the use of cannabidiol. Significant adverse effects related to appetite or sleep were only observed in 42% of patients following the use of cannabidiol (31).

3. Genetic variations associated with pharmacoresistant epilepsy

Previous studies have suggested that pharmacokinetic and pharmacodynamic mechanisms form the physiopathological basis of pharmacoresistant epilepsy (Table I) (22,32,33). Advances in genomic technologies have facilitated the genome-wide discovery of common and rare variants and have increased our understanding of genetics in epilepsy (34); however, the mechanisms underlying pharmacological resistance have not been fully elucidated (35). Some of the most important genes associated with the physiopathology of epilepsy were associated with the neuronal acetylcholine receptor, neuronal potassium channels (KCNs), voltage-dependent sodium channels (SCNs), calcium channels and \( \gamma \)-aminobutyric acid (GABA) receptors (32,36,37). Table II summarizes some of the genetic variants that occur in the main genes linked to epilepsy from recent studies.

In the particular case of pharmacoresistant epilepsy, the most frequently studied polymorphisms are those associated with multidrug resistance genes (MDR): ATP-binding cassette subfamily B member 1 (ABCB1) or MDR1 and ATP-binding cassette subfamily C member 2 (ABCC2 or MRP2); SCN\( \alpha \) subunits 1, 2 and 3 (SCN1, SCN2 and SCN3); and metabolizers of endogenous and xenobiotic substances, cytochromes P450 families 2 and 3 (CYP2 and CYP3). Additional details related to the findings of these studies are found in Table III.

4. The role of genetic variants in the diagnosis and treatment of pharmacoresistant epilepsy

Currently, a patient's medical history and EEG results are used to diagnose the type of seizure, but they must be interpreted with caution so that diagnostic errors are not made; this suggests the use of complementary studies (38). Emerging genomic technologies, high-throughput screening and chip technologies have accelerated our understanding of the genetic makeup of epilepsy (34); for instance, the identification of mutations or polymorphisms in specific genes, such as those that encode ion channels, aforementioned, that are mainly expressed in brain neurons, specific neurotransmitter receptors and molecules that have functions in intercellular communication (39). For example, a study by Wang et al (40) investigated the genetic etiology of epilepsy in a cohort of 120 children with unexplained epilepsy using whole-exome sequencing (WES); it was found that the pathogenic variant c.174G>A in the KCN subfamily D member 3 (KCNBD3) gene may be responsible for a broader phenotypic spectrum than was previously thought, including infantile epileptic encephalopathy. In addition, this study discovered that the glutamate receptor, ionotropic glutamate ionotropic receptor NMDA-type subunit 1 (GRIN1) and hyperpolarization-activated cyclic nucleotide-gated potassium channel 1 (HCN1), were candidate gene variants (c.2530C>T and c.1138A>T for GRIN1 and HCN1, respectively) for the Dravet and Dravet-like phenotypes (40). In intractable epilepsy and other mental disabilities, WES identified de novo variants in the Bernardinelli-Seip congenital lipodystrophy 2 (BSCL2) gene in two patients (41), of which one of the variants (c.985C>T) has been observed in other populations of epilepsy and developmental regression, regressive autism spectrum disorder, motor stereotypies, lower limb hypertonia and frontal lobe syndrome (41). As it was discovered that BSCL2 serves a role in neuronal function, it was suggested to be a potential candidate gene for epileptogenesis (41).

In pyrodoxine-dependent epilepsy (PDE), despite seizure control, 2.75% of patients experience intellectual disability and developmental delay, which emphasizes the importance of early diagnosis. Genetic tests are increasingly being used as first-level tests for epileptic encephalopathies, which aim to provide a general description of the mutations in the aldehyde dehydrogenase 7 family member A1 that causes PDE (42). Epilepsy with myoclonic-atactic seizures (EMAS) accounts for 1-2% of all childhood onset epilepsies (43). EMAS has been demonstrated to have an underlying genetic component and several genes have been associated with this disease, such as SCN1A, SCN2A, CHD2, STX1B, SLC2A1, SLC6A1, POLG1, NRXN1, PIGN, CSNK2A1, GABRG2 and GABRB3; however, the genetic basis for this disorder remains unknown and the diagnostic potential of genetic tests remains low. This could be explained by the lack of several of the genes that may be associated with EMAS in the most commonly ordered epilepsy panels, although some have recently been added (43-47). Furthermore, a study conducted by Ortega-Moreno et al (48) analyzed a multigenic panel of 87 PWE and developmental delay, including classified and unclassified epileptic encephalopathies, epileptic spasms, severe myoclonic epilepsy of infancy, Lennox-Gastaut and Landau-Kleffner syndromes; they found mutations in various genes, such as potassium voltage-gated channel subfamily Q member 2 (KCNQ2), syntaxin binding protein 1, UDP-N-acetylglucosaminyltransferase subunit, cyclin dependent kinase-like 5 (CDKL5), protocadherin 19, SCN1A, CHD2, SLC2A1, synaptic Ras GTPase activating protein 1, aristless related homeobox, DNA polymerase gamma, catalytic subunit and GRIN1. Although a high proportion of these patients had unclassified epilepsies, the results supported the use of the multigene epilepsy panel because it offered rapid testing with a good diagnostic efficiency (48).

It is hypothesized that genetic variants may also contribute to the efficacy of drug treatments for epilepsy; for example, adverse or toxic reactions, teratogenic risk in pregnancy, as well as long-term outcomes have been observed among PWE (49-63). Consistent with the findings in numerous other disorders with complex genetic backgrounds, the associated genetic variants that have been successfully verified are limited. Nevertheless, it is likely that new techniques and improved research approaches will increase this number in the near future (49). In recent studies, the association between genetic polymorphisms, treatment responses in epilepsy and AEDs reactions (toxic, adverse or those related with its efficacy) have been investigated; it was reported that polymorphisms in the human leukocyte antigen (HLA) gene
were associated with severe cutaneous adverse AED reactions (50), and polymorphisms in a number of other genes, including ABCB1, ABCG2, GABRA6, GABRG2, CYP2C9, CYP3A4, UDP-glucuronosyltransferase (UGT)1A1, UGT1A4, UGT1A6, UGT2B7, SCN2A and SCN1A, have been associated with the concentration, response and efficacy of some of the most commonly used AEDs in clinical practice, including carbamazepine, oxcarbazepine, phenytoin, lamotrigine and valproic acid (51-63). Esmaeilzadeh et al (50) reported an association between HLA polymorphisms and severe cutaneous adverse reactions (SCARs) induced by drugs; in this study, 61 patients with diverse SCARs were recruited, and it was found that the hypersensitivity to different AEDs, including phenytoin, carbamazepine, valproic acid, topiramate and lamotrigine, was associated with HLA-A gene polymorphisms. Berghuis et al (64) recruited 1,328 adult PWE who had received oxcarbazepine (n=1,031) and carbamazepine (n=297) and performed a genome-wide association study to demonstrate the association between genetic factors and sodium levels and AED metabolism. The authors did not observe significant associations between sodium levels and other clinical variables, but in relation to carbamazepine metabolism, they observed a significant association with the intronic rs2234922 polymorphism in the epoxide hydrolase 1 gene. Furthermore, the same authors reported in 2017 that the rs119419784 polymorphism and an intronic variant of the leptin receptor gain. in another study conducted by Li et al (67), it was found that VPA induced obesity in PWE, as following the recruitment of 225 Chinese Han patients with epilepsy receiving VPA treatment, 19.6% were found to be obese. The authors also found genotypic associations of rs11941979 in the CD36 gene and rs10865710 in the peroxisome proliferator-activated receptor γ gene following weight gain. In another study conducted by Li et al (68), associations between the rs1137101 polymorphism in the leptin receptor (P<0.001), the rs1800497 polymorphism in the ankyrin repeat kinase domain-containing 1 (P=0.017) and the rs10789038 polymorphism in AMP protein kinase (P=0.02) with valproic acid-induced weight gain were observed in 212 PWE (68). Wang et al (69) discovered that some polymorphisms were associated with the adverse effects of valproic acid in Chinese PWE by direct sequencing; following the recruitment of 254 Chinese PWE that received valproic acid monotherapy, a correlation was identified between CYP2C9 and acyl-coenzyme A synthetase 2A (ACSM2A) gene polymorphisms with serum alanine aminotransferase and aspartate aminotransferase levels (P<0.03) indicating that these gene polymorphisms can be used to identify liver dysfunction (69).

The therapeutic effect of valproic acid among children with focal epilepsy (89 children) was also studied, and the results identified 66 single nucleotide polymorphisms (SNPs) that were involved in the metabolism and transport of valproic acid target receptors (54); however, among the children with

### Table I. Mechanisms associated with pharmacoresistant epilepsy.

| Mechanism | Description |
|-----------|-------------|
| Pharmacokinetics | Impairment of the AED to achieve optimal concentration levels at the action site, where it is mainly influenced by the liposolubility, absorption, metabolism and elimination of the drug. |
| Pharmacodynamics | All the factors that alter the action of the AED in their action sites (synapses, ion channels and receptors). There are at least three hypotheses that try to explain the pharmacodynamics: i) Alterations involving transporters (i.e. P-glycoprotein and the multiple drug resistance gene); ii) modifications of pharmacological targets due to genetic alterations related to the disease (i.e. genetic alterations in receptors or ion channels, structural alterations, autoimmunity and pharmacological interactions); iii) the intrinsic gravity model of epilepsy, in which a continuous severity of the disease is proposed and will be determined due to the medication response (i.e. etiology of epilepsy, type of seizures, electroencephalography or imaging studies, environmental influences or failure of AED). |

Adapted from Refs. 22,83,84. AED, antiepileptic drug.

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Table II. Variations in the main genes associated with the physiopathology of epilepsy.

| Author, year                  | Gene observations | Observations                                                                 | (Refs.) |
|-------------------------------|-------------------|-------------------------------------------------------------------------------|---------|
| Trivisano et al, 2015         | Cholinergic receptor α2 subunit mutation has been described in benign familial infantile seizures (c.1126 C>T). | (85)    |
| Wang et al, 2014; Villa et al, 2019 | Cholinergic receptor α4 subunit The novel mutation c.823 A>T has been identified in non-familial nocturnal frontal lobe epilepsy. The c.754T>C mutation is involved in autosomal dominant nocturnal frontal lobe epilepsy. | (86,87) |
| Goldberg-Stern et al, 2009; Chen et al, 2018; Allen et al, 2014 | KCNQ2 The novel mutation c.63-66delGGTG was associated with the diagnosis and prognosis of BFNS. Two mutations, c.811C>T and c.875T>C, were with early infantile encephalopathies. | (88-90) |
| Allen et al, 2014; Piro et al, 2019; Miceli et al, 2015 | KCNQ3 The novel mutation c.914A>T was related to BFNS and was associated with a specific electroclinical pattern and favorable neurodevelopmental outcomes. The mutation c.989G>T was associated with intellectual disability in BFNS and the mutation c.989G>A was also associated with this type of epilepsy. | (90-92) |
| Lehman et al, 2017 | KCNQ5 Three mutations, c.1343G>T, c.434T>G and c.1021C>A, were associated with epileptic encephalopathy and caused intellectual disability. | (93)    |
| Krepischi et al, 2010 | SCN1A The deletion in 2q24, del(2)(q24.2q24.3), was associated with Dravet syndrome. | (94)    |
| Liang et al, 2017 | SCN2A The novel mutation c.1270G>A was associated with early-onset epileptic encephalopathy and Rett-like features. | (95)    |
| Davidsson et al, 2008 | Gene cluster (SCN1A-SCN2A-SCN3A-SCN7A-SCN9A) The deletion in 2q24, del(2)(q24.3q31.1), was associated with severe epilepsy of infancy (Dravet syndrome) and was correlated with dysmorphic features and brain abnormalities. | (96)    |
| Zaman et al, 2018 | SCN3A Mutations have been associated with early infantile epileptic encephalopathy. | (97)    |
| Yang et al, 2019; Butler et al, 2018; Orenstein et al, 2018; Zhang et al, 2017; Hernandez et al, 2017; Farnaes et al, 2017; Iqbal et al, 2018; Bhat et al, 2018; Le et al, 2017; Ishii et al, 2017 | GABA_A The presence of various variants was associated with multiple seizure types, including focal seizures, generalized tonic-clonic seizures, myoclonic seizures, epileptic spasm and Dravet's syndrome, Ohtahara syndrome and West syndrome. De novo variants in GABRA2 (c.875C>A and c.1003A>C), GABRA5 (c.880G>C) and GABRB3 (c.5G>A, c.509T>G, c.914C>T and c.863C>A) were associated with severe early onset epilepsy. The de novo mutation c.789G>A in GABRA1 was associated with West syndrome. Mutational analysis of GABRG2 found an association between the presence of a single polymorphic site in exon 3 (AAC>AAT) and the absence epilepsy and generalized tonic clonic seizures. Variants in GABRG2 (588C>T) and GABRD (659G>A) were associated with juvenile myoclonic epilepsy and Lennox-Gastaut syndrome. The mutation 965C>A and the polymorphism 15A>G in GABRA1 were associated with Lennox-Gastaut syndrome. The de novo mutation c.695G>A in GABRB3 was associated with Dravet syndrome The de novo mutation c.859A>C in GABRB2 was associated with early myoclonic encephalopathy. | (98-107) |
focal seizures, the selected genetic polymorphisms were not significantly associated with the response to valproic acid. Nonetheless, three variants of GABRA6 (rs9313892, rs4921195 and rs424740) demonstrated the potential to be associated with the response to valproic acid (54). In addition, although polymorphisms in the SCN1A gene are thought to influence the efficacy of carbamazepine and phenytoin, Manna et al (70) found that the rs3812718 variant in SCN1A was not associated with the response to carbamazepine in patients with focal epilepsy. It has been reported that disorders related to changes in the KCNQ2 gene included both benign seizure disorders and early onset epileptic encephalopathies (EOEE), especially the latter, which includes patients who present refractory seizures following standard AED treatment and development delay (71-73). Kuersten et al (74) conducted a systematic review (52 studies including data from 217 patients), in which they analyzed AEDs in KCNQ2-related epilepsies; it was discovered that seizures associated with KCNs could be controlled upon treatment with carbamazepine, lamotrigine, oxcarbazepine, phenytoin, valproic acid, levetiracetam, topiramate, phenobarbital, piracetam, vigabatrin, clonazepam, diazepam and midazolam in patients with benign infantile or neonatal seizures (n=133 patients, including 74 who were seizure-free following monotherapy, 4 who were unsuccessfully treated with monotherapy, 11 who were seizure-free with polytherapy, 4 patients with no response to polytherapy or any treatment and 40 showed seizure cessation spontaneously without AEDs). Moreover, the results also demonstrated that moderate control of seizures was achieved with the use of carbamazepine, oxcarbazepine, lamotrigine, lacosamide, phenytoin, phenobarbital, valproic acid, topiramate, levetiracetam, retigabine, zonisamide, sulfiame, ethosuximide, acetazolamide, clonazepam, diazepam, clobazam, nitrazepam and midazolam in patients with EOEE (n=84, including 48 who were seizure-free with monotherapy, 12 that did not respond to monotherapy, 20 who were seizure-free following polytherapy and 4 patients exhibited seizure reduction without AED). Phenobarbital was the most common prescribed monotherapy in the majority of patients with benign seizures and EOEE (n=65 in benign seizures and n=35 in patients with EOEE); however, the use of sodium channel blockers, such as carbamazepine, lamotrigine, oxcarbazepine and phenytoin, led to seizure cessation in the majority of patients with benign seizures and EOEE (n=21 benign seizures and n=45 with EOEE). With regards to the genetics, 25.6 and 67.9% of patients with benign seizures and EOEE, respectively, were reported to have de novo mutations, including missense, frameshift, splice site, deletion and truncation mutations. However, sparse systemic data are available on the response of treatment in KCNQ2-related epilepsy in larger cohorts (74), which limit our ability to comment on the efficacy of personalized medicine approaches to treat the large number of newly discovered genetic channelopathies.

The effects of SNPs in three KCN genes, including KCNAl (rs12561866, rs2227910 and rs7974459), KCN2A (rs3887820) and KCN2V (rs7029012, rs10967705 and rs10967728), and their association with the susceptibility to epilepsy and their ability to respond to AEDs (carbamazepine for partial epilepsy and valproic acid for generalized epilepsy) was analyzed in a pharmacoepidemiologic cohort of 595 patients (75). The results suggested that KCNAl, KCN2A and KCN2V did not influence the susceptibility of the disease or the capacity to respond to drugs (75). Mutations in the SCN2A gene have also been associated with neonatal seizures and a wide number of epileptic syndromes (76,77). Recently, an association between rs17183814 in SCN2A and the function of oxcarbazepine was demonstrated in a cohort of 218 patients; the results indicated that the presence of the SNP was associated with higher oxcarbazepine maintenance doses in patients with lower
Table III. Genes associated with pharmacoresistant epilepsy.

| Author, year               | Gene                                      | Main observations                                                                 | (Refs.) |
|----------------------------|-------------------------------------------|-----------------------------------------------------------------------------------|---------|
| Yoshida et al, 2018        | BAF chromatin remodeling complex subunit BCL11A | Japanese patients with epileptic encephalopathy.                                 | (116)   |
| Kurian et al, 2018         | PCDH19                                    | Mutations were determined in pediatric patients with pharmacoresistant early childhood epilepsy. | (117)   |
| Ko et al, 2018             | SCN1A, CDKL5, KCNQ2, SCN2A and SCN8A       | Mutations were determined in Asian patients with epileptic syndromes.            | (118)   |
| Wang et al, 2018; Feng et al, 2018; Margari et al, 2018 | SCN1A and CYP5A4                  | Polymorphisms were associated in Chinese children and adults with drug-resistant generalized epilepsy treated with valproic acid monotherapy. Also, polymorphisms in the SCN1A gene were associated with pharmacoresistance in Italian pediatric patients with epilepsy. | (58,119,120) |
| Ajmi et al, 2018           | ABCB1                                     | Polymorphisms increased the risk of developing drug resistance in Tunisian epileptic patients. | (121)   |
| Abou El Ella et al, 2018   | GABR γ2 subunit                           | Polymorphisms were associated with pharmacoresistance in Egyptian children with idiopathic generalized epilepsy. | (122)   |
| Skalski et al, 2017        | MDR1                                      | Polymorphisms were not associated with pharmacoresistance in Polish patients with refractory epilepsy. | (123)   |
| López-Garcia et al, 2017   | CYP2D6, CYP2C9, CYP2C19 and CYP3A4        | Polymorphisms were associated with refractory epilepsy in Mexican pediatric patients. | (124)   |
| Lv et al, 2017             | CACNA1A                                   | Mutations were identified in Chinese patients with refractory progressive myoclonic epilepsy. | (125)   |
| Kozera-Kępniak et al, 2017 | Nuclear receptor subfamily 1 group I member 2 | Polymorphisms were associated with pharmacoresistance in Polish epileptic patients. | (126)   |
| Wang et al, 2017           | SCN8A                                     | Mutations were identified in Chinese family with epilepsy.                       | (127)   |
| Parrini et al, 2017        | KCNA, KCNB, GABR and PNPO                | Mutations were identified in Italian children diagnosed with several types of pharmacoresistant epilepsy. | (128)   |
| Kimizu et al, 2017         | SLC35A1                                   | A mutation was identified in a female Japanese pediatric patient with hepatic encephalopathy. | (129)   |
| Shen et al, 2017           | GABRG2                                    | Mutations were identified among Caucasian patients with epileptic encephalopathy. | (130)   |
| Zhang et al, 2017; Miao et al, 2017 | CDKL5, KCNQ2, KCNT1, KCNB1 SCN2A, SCN8A and SLC2A1 | Mutations were identified in Chinese patients diagnosed with pharmacoresistant epilepsy. | (131,132) |
| Perucca et al, 2017        | SCN1A                                     | A variant was identified in an Australian patient with pharmacoresistant temporal lobe epilepsy. | (133)   |
| Guo et al, 2016            | Advanced glycosylation end-product specific receptor | Variants were discovered in Chinese patients and associated with pharmacoresistant temporal lobe epilepsy. | (134)   |
| Stasiołek et al, 2016      | MDR1                                      | Variants were identified in Polish children diagnosed with refractory epilepsy.   | (135)   |
| Abo El Fotoh et al, 2016   | SCN1A and CYP3A5                           | Polymorphisms were associated with pharmacoresistance in pediatric patients with refractory idiopathic and symptomatic epilepsy. | (136)   |
| Author, year | Gene | Main observations | (Refs.) |
|-------------|------|------------------|---------|
| Xue and Lu, 2016 | ABCB1 and ABCC2 | Variants were identified in Chinese patients with refractory symptomatic epilepsy and associated with pharmacoresistance. | (137) |
| Moen et al, 2016 | Potassium channel tetramerization domain containing 7, Sonic hedgehog signaling molecule, Smoothened, frizzled class receptor, Wnt16 and Wnt2 | A mutation was discovered in an Arab family with two children with pharmacoresistant progressive myoclonic epilepsy. | (138) |
| Hildebrand et al, 2016 | Genes related to the Shh way | Mutations were found in Caucasian patients with gelastic epilepsy. | (139) |
| Hardies et al, 2016 | Synaptojanin 1 | Authors analyzed patients from three Caucasian families who had been treated for refractory seizures and progressive neurological diseases. Variants that abolished enzymatic activity were identified. | (140) |
| Lionel et al, 2016 | Mediator complex subunit 23 | A variant was identified in a pediatric patient with refractory epilepsy. | (141) |
| Balestrini et al, 2016 | TBC1 domain family member 24 | Mutations were analyzed in patients with pharmacoresistant epilepsy from 30 independent families. Pathogenic mutations were identified in the first conserved motif, some of which were associated with epileptic syndromes. | (142) |
| Fahrner et al, 2016; Vanstone et al, 2016 | Dynamin 1-like | A mutation was determined in two American pediatric patients with epileptic encephalopathy and a variant was determined in a Canadian female pediatric patient diagnosed with epileptic encephalopathy. | (143,144) |
| Janssen et al, 2016 | DNA polymerase γ catalytic subunit | Mutations were found in Belgian patients with refractory epilepsy and status epilepticus. | (145) |
| Li et al, 2016 | GRIN2D | A mutation was found in children with epileptic encephalopathy (one patient was African American and had European descent and the other patient was from Tunisia). | (146) |
| Segal et al, 2016; Palmer et al, 2016 | SCN1A, PCDH19, SLC6A1 and SLC9A6 | Mutations were found in American children with pharmacoresistant epilepsy along with significant clinical abnormalities. An SLC6A1 mutation was specifically discovered in an American female pediatric patient with Doose syndrome. | (147,148) |
| Inui et al, 2016 | Eukaryotic translation elongation factor 1 α2 | A mutation was found in Japanese patients with epileptic encephalopathy. | (149) |
| Horta et al, 2015 | Major histocompatibility complex, class II, DR β1 | Variants were found in patients with pharmacoresistant temporal lobe epilepsy. | (150) |
| Damiano et al, 2015 | Lamin B2 | A mutation was found in 10 patients with epilepsy who were members of an Arab-Palestinian family with a history of pharmacoresistant autosomal progressive myoclonic epilepsy with early-onset ataxia. | (151) |
| Bene et al, 2015; Berghuis et al, 2015 | SCN1A and SCN8A | Mutations were identified in a Hungarian pediatric patient with Dravet syndrome. A mutation in the SCN8A gene was discovered in a Norwegian patient with epileptic encephalopathy. | (152,153) |
| Damaj et al, 2015 | CACNA1A | A mutation was determined in Franco-Canadian families with members diagnosed with epileptic encephalopathy. | (154) |
| Author, year | Gene | Main observations | (Refs.) |
|-------------|------|------------------|--------|
| Guo et al, 2015 | *KCNJ10* | Variants were determined in Chinese patients with refractory genetic generalized epilepsy. | (155) |
| Liu et al, 2015 | Kelch-like ECH associated protein 1, nuclear factor, erythroid 2-like 2 | Variants were determined in patients with pharmacoresistant temporal lobe epilepsy and associated with pharmacoresistance. | (156) |
| Emich-Widera et al, 2014 | *ABCB1*; also known as *MDR1* | A variant was determined in Polish pediatric patients with refractory partial epilepsy. | (157) |
| Venkateswaran et al, 2014 | *GRIN2A* | A mutation was found in a female Canadian pediatric patient with refractory epilepsy. | (158) |
| Picard et al, 2014 | DEP domain containing 5, GATOR1 subcomplex subunit | Mutations were identified in Caucasian individuals diagnosed with dominant nocturnal temporal lobe epilepsy. | (159) |
| Martin et al, 2014 | *KCNQ2*, *SCN2A* and *KCNT1* | Mutations were identified in Caucasian patients with severe early-onset epilepsy. | (160) |
| Seven et al, 2014; Escalante-Santiago et al, 2014 | *MDR* and *MRP2* | Variants were identified among Turkish pediatric patients with refractory partial and generalized epilepsy. Variants in this genes were also identified in 22 Mexican children diagnosed with refractory partial complex epilepsy | (161,162) |
| Seven et al, 2014 | *CYP2C9*, *CYP2C1* and *CYP2D6* | Polymorphisms were determined in Turkish pediatric patients with partial epilepsy or refractory generalized epilepsy and associated with pharmacoresistance. | (163) |
| Ma et al, 2014 | *SCN1A*, *SCN2A* and *ABCC2* | Variants were analyzed in Chinese patients with refractory partial or generalized epilepsy and associated with pharmacoresistance. | (164) |
| He et al, 2013 | C-C motif chemokine ligand 2 | A variant was determined in Chinese children with refractory partial and generalized epilepsy and associated with pharmacoresistance. | (165) |
| Serino et al, 2013 | *KCNQ2* | A mutation was found in an Italian pediatric patient with epileptic encephalopathy. | (166) |
| Emich-Widera et al, 2013 | *CYP3A5* and *MDR1* | A variant was found in Polish children diagnosed with refractory epilepsy. | (167) |
| Veeramah et al, 2013 | *CDK*, chloride voltage-gated channel 1, *SCN*, *KCNH* | Mutations were identified in the families of American children diagnosed with epileptic encephalopathy. | (168) |
| Fragaki et al, 2013 | Glutamate receptor, metabotropic 6 | A mutation was identified in the family of two French pediatric patients with refractory epilepsy. | (169) |
| Subenthiran et al, 2013; Qu et al, 2012 | *ABCB1* and *ABCC2* | Variants were associated with pharmacoresistance in Malaysian (49.7%), Chinese (26.8%) and Indian (23.5%) adult patients with epilepsy with complex partial seizures treated with carbamazepine. Variants were also found in Chinese patients with partial idiopathic or refractory cryptogenic epilepsy and associated with pharmacoresistance. | (170,171) |
| Dimova et al, 2012 | *PCDH19* | A mutation was identified in one female pediatric patient with refractory epilepsy. | (172) |
| Author, year     | Gene       | Main observations                                                                                                                                                                                                 |
|------------------|------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sayyah et al, 2011 | ABCB1      | Variants were identified in Iranian children and adults diagnosed with refractory idiopathic, cryptogenic and symptomatic epilepsy and associated with pharmacoresistance.                                             |
| Lakhan et al, 2011 | CYP2C9 and CYP2C19 | Variants were determined in Indian patients with refractory idiopathic and symptomatic epilepsy.                                                                                                                                 |
| Kumari et al, 2011 | SCN2, GABR | Variants were identified in Indian patients diagnosed with refractory epilepsy and associated with pharmacoresistance.                                                                                           |
| Kwan et al, 2011  | ABCC2, ABCC5 and ABCG2 | Polymorphisms were analyzed in Chinese patients with refractory epilepsy.                                                                                                                            |
| Kim et al, 2011   | SLC6A11    | Variants were found in Korean patients with refractory idiopathic, symptomatic and cryptogenic epilepsy and associated with pharmacoresistance.                                                               |
| Meng et al, 2011  | SLC6A11    | Variants were found in Chinese patients with drug-resistant focal and generalized epilepsy and treated with carbamazepine monotherapy.                                                                          |
| Alpman et al, 2010 | MDR1       | Variants were determined in Turkish pediatric patients with refractory generalized or partial epilepsy.                                                                                                   |
| Maleki et al, 2010 | ABCB1      | Variants were determined in Iranian pediatric and adults with refractory idiopathic and symptomatic epilepsy and associated with pharmacoresistance.                                                             |
| Di Bonaventura et al, 2009 | Leucine rich glioma inactivated 1 | A mutation was determined in an Italian family with refractory autosomal dominant lateral temporal lobe epilepsy.                                                                                      |
| Jang et al, 2009  | SCN1A, SCN1B and SCN2A | Variants were determined in Korean patients with refractory symptomatic and idiopathic epilepsy.                                                                                                                                 |
| Vahab et al, 2009; Kwan et al, 2009 | ABCB1 | Variants were determined in Indian pediatric patients with refractory epilepsy, in Chinese patients with refractory idiopathic, symptomatic or cryptogenic epilepsy and were associated with pharmacoresistance. |
| Kauffman et al, 2009 | SLC6A4     | A variant was determined in adult Argentine patients with drug-resistant mesial temporal lobe epilepsy and associated with pharmacoresistance.                                                              |
| Lakhan et al, 2009 | SCN1A and SCN2A | A variant was determined in Indian patients with drug-resistant epilepsy and associated with pharmacoresistance.                                                                                      |
| Bahi-Buisson et al, 2008 | CDKL5      | Mutations were identified in female Caucasian patients with Rett syndrome with refractory epilepsy.                                                                                                                                 |
| Kwan et al, 2008  | SCN1A, SCN2A and SCN3A | Variants were identified in Chinese patients with refractory symptomatic, idiopathic and cryptogenic epilepsy and associated with pharmacoresistance.                                                             |
| Elia et al, 2008  | CDKL5      | Mutations were analyzed in Italian children with profound mental retardation and seizures (myoclonic or tonic spasms) that were refractory to treatment. A total of three de novo missense mutations were identified in the gene. |
| Abe et al, 2008   | SCN1A      | A variant was identified in Japanese drug-responsive epileptic patients and associated with pharmacoresistance.                                                                                           |
| Shahwan et al, 2007; Kwan et al, 2007; Hung et al, 2007 | ABCB1 | Variants were determined in Irish and in Chinese adult patients with refractory epilepsy. A logistic model revealed that the interaction of the polymorphisms was associated with drug-resistant epilepsy after adjusting for etiology and type of epilepsy in Chinese patients. |
Leschziner et al, 2007  | rala binding protein 1 | Variants were genotyped in English patients with drug-resistant epilepsy associated with pharmacoresistance. A total of six SNPs were genotyped displaying an association between rs329017 and the risk of pharmacoresistance. | (194) 
Seo et al, 2006; Hung et al, 2005  | ABCB1 | Variants were genotyped in patients with epilepsy and associated with pharmacoresistance. Haplotype analysis indicated that drug-resistant patients tended to display CGC/CGC, CGC/TGC, CGC/TTT and TGC/CGT combinations. | (195,196) 
Mills et al, 2005  | PNPO | Mutations in Asian families with epileptic encephalopathy were determined. | (197) 
Buono et al, 2004  | KCNJ10 | A variant was detected in Caucasian patients diagnosed with refractory mesial temporal lobe epilepsy and associated with pharmacoresistance. | (198) 
Siddiqui et al, 2003  | ABCB1 | A variant was identified in English patients with refractory epilepsy and associated with pharmacoresistance. | (199) 
Gambardella et al, 2003  | GABA_B receptor 1 | A variant was determined in Italian patients with temporal lobe epilepsy and associated with pharmacoresistance. | (200) 

ABC1, ATP binding-cassette subfamily B member 1; ABCC2, ATP binding-cassette subfamily C member 2; ABCC5, ATP binding-cassette subfamily C member 5; ABCC2, ATP binding-cassette subfamily G member 2; CACNA1A, calcium voltage-gated channel subunit α 1A; CYP2C19, cytochrome P450 family 2 subfamily C member 1; CYP2C19, cytochrome P450 family 2 subfamily C member 19; CYP2C9, cytochrome P450 family 2 subfamily C member 9; CYP2D6, cytochrome P450 family 2 subfamily D member 6; CYP3A5, cytochrome P450 family 3 subfamily A member 5; CYP3A4, cytochrome P450 family 3 subfamily A member 4; GABA, γ-aminobutyric acid receptor; GABR, γ-aminobutyric acid type A receptor; GRIN2, glutamate ionotropic receptor NMDA-type subunit 2; KCNA, potassium voltage-gated channel subfamily A; KCNB, potassium voltage-gated channel subfamily B; KCNH, potassium voltage-gated channel subfamily H; KCNJ10, potassium inwardly rectifying channel subfamily J member 10; KCNT1, potassium sodium-activated channel subfamily T member 1; MDR1, ABC transporter B family member 1; PNPO, pyridoxamine 5′-phosphate oxidase; SCN2A, sodium voltage-gated channel α subunit 2; SCN3A, sodium voltage-gated channel α subunit 3; SCN8A, sodium voltage-gated channel α subunit 8; SCN1B, sodium voltage-gated channel β subunit 1; SLC35A1, solute carrier family 35 member A2; SLC6A1, solute carrier family 6 member 1; SLC6A4, solute carrier family 6 member 4; SLC6A11, solute carrier family 6 member 11; SLC9A6, solute carrier family 9 member 6.

body weights and lower oxcarbazepine maintenance doses in patients who were overweight (51). In a cohort of 201 patients treated with valproic acid, an association was reported between the presence of the SNP rs230416 in SCN2A and the response to the drug (78). Similarly, another study reported an association between the SNPs in SCN2A (rs2304016) and SCN3B (rs3851100) and AED responsiveness in a cohort of 595 patients who were treated with valproic acid for generalized epilepsy and carbamazepine for partial epilepsy; the results demonstrated that none of these SNPs were significantly associated with a response to the AED (79).

Previous studies have indicated that to improve the efficacy and safety of epilepsy treatments, it is necessary to conduct studies to identify the following: i) The possible influence of some of the phenotypic characteristics of patients in response to the treatments; ii) the relationship between the number and type of seizures; iii) the differences in drug transporting protein activity or receptor activity caused by the genetic variations; iii) the impact of the presence of a genetic variant on the functionality of transporting proteins and AED target proteins; iv) the effects of potential alterations in target proteins, owing to a genetic variant, in the mechanisms of action of an AED; and v) factors that may contribute to susceptibility and treatment outcomes.

5. Clinical implications of genetic variants in pharmacoresistant epilepsy

Personalized medicine is treatment of patients with therapy aimed at targeting their specific pathophysiology; however, currently, this has limited applications in clinical practice. Advancements in genetic epilepsy models and deep phenotyping techniques have the potential to revolutionize translational research, and will bring precision medicine to the forefront of clinical practice (80). In a needs assessment aimed at identifying the clinical challenges faced by physicians in diagnosing and treating children with epilepsy in Germany, Spain and the United States, it was reported that the main challenges were the application of guidelines in clinical practice, the identification of epilepsy and epileptic events, the integration of genetic tests into clinical practice, the integration of non-pharmaceutical treatments, the transition from pediatric to adult care and the participation and
commitment of caregivers (80). These findings may support neuropsychiatrists who wish to specialize in epileptology to address these identified challenges based through precision medicine treatments (80). As we continue to gain an improved understanding of the true complexity underlying the physio-pathology of genetic epilepsy and the identification of factors that are involved in phenotypic variations, it will be easier to address and understand genotype-phenotype correlations (81).

Previous studies on genetic epilepsy syndromes have provided insight into the mechanisms of epileptogenesis, and have suggested roles for a number of genes with different functions, including ion channel proteins and those associated with the synaptic vesicle cycle and energy metabolism (82). In addition, advanced genomic technologies, high-throughput sequencing and molecular diagnostics are increasingly improving our understanding of the genetic architecture in epilepsy, and molecular confirmation may influence the treatment prescribed for some monogenic epilepsies. Moreover, it is of crucial importance that genetic methods that are able to analyze all known genes at a reasonable cost be developed to discover novel therapeutic options and to implement individualized precision medical treatment regimens (82).

6. Conclusions and future perspectives

Genetic variations in the most common genes that encode channels, transporters, drug-metabolizing enzymes and receptors have been discussed in this Review with regards to their association with drug-resistant epilepsy, including: Sodium voltage-gated channels SCN1A, SCN2A, SCN3A, SCN8A and SCN1B; potassium voltage-gated channels (KCNAA1, KCNA2, KCNB1, KCNBD7, KCNHI5, KCNJ10, KCNQ2 and KCNT1); calcium voltage-gated channel subunit α1 H; ATP binding-cassette transporters (ABCB1, ABCB2, ABCB5 and ABCG2); mitochondrial transporter family members (SLC2A1, SLC6A1, SLC6A4, SLC6A11, SLC9A6, SLC25A22 and SLC35A2); drug-metabolizing enzymes (CYP2C1, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5); CCKL5; and GABA receptors (GABRA1 and GABBR1). These data may prove useful for future studies of drug resistance in epilepsy and may contribute to the generation of new diagnostic methods. In addition, these methods could subsequently support the development of improved treatment regimens, including novel pharmacological targets and pharmacological therapeutics. Overall, these findings may also improve the application of pharmacological targets and pharmacological therapeutics.

This development of improved treatment regimens, in addition, these methods could subsequently support the generation of new diagnostic methods. In addition, these methods could subsequently support the development of improved treatment regimens, including novel pharmacological targets and pharmacological therapeutics. Overall, these findings may also improve the application of pharmacological targets and pharmacological therapeutics.

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Authors' contributions

LCA, DLPL, SGM and IIM wrote and revised the manuscript; DOC critically revised and corrected the manuscript; and NCR conceived the idea for the review, collected and interpreted the studies included, reviewed the manuscript and contributed significantly to the writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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