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Genetic Polymorphisms in Patients with Epilepsy: A Mini Review.

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Abstract

Epilepsy comprises a series of chronic neurological disorders characterized by recurrent seizures. Over 50 million people are affected by epilepsy worldwide. In addition, genetic components capable of predicting epilepsy predisposition and antiepileptic drugs response would lead to the development of promising treatment and a better prognosis of the disease. Several genes and their variants have been investigated whether they could affect the onset of epilepsy. The brain-derived neurotrophic factor gene, the ATP-binding cassette subfamily B member and the cytochrome P450 are the most common polymorphic genes related to epilepsy. Early identification of risk factors for epilepsy should optimize treatment and prognosis. The characterization of genetic polymorphism contribute to the selection of the most promising antiepileptic therapy and avoidance of drug resistance. The development of biomarkers to estimate the risk of epilepsy and drug resistance would have a clinical impact on the treatment of the disease and on anti-epileptic drug therapy.

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Introduction

Epilepsy comprises a series of chronic neurological disorders characterized by seizures. Epileptic seizures are related to abnormal and uncontrolled neuronal activity of the brain. It is the most common neurological disorder after stroke [1]. Seizures are normally recurrent with no immediate primary cause, but genetic abnormalities could be one of the possible causes [2]. Genetic mutations can lead to the onset of epilepsy [3]. Epilepsy can occur as the result injuries to the nervous system, stroke, tumors or infection [4]. Epidemiological studies have shown that over 50 million people are affected by epilepsy worldwide [5] and the treatment focus initially on seizure suppression or prorogation [6].

One of the most important pathophysiology of epilepsy is the blood brain barrier (BBB) permeability. It is known that BBB contributes to epileptogenesis in symptomatic epilepsies. Genetic components that predict epilepsy predisposition and antiepileptic drugs response would lead to the development of promising treatment and a better prognosis of the disease [7]. The onset of epilepsy can be directly or indirectly linked to genetic disorders. It could be related to a single gene, a combination of genetics and environmental factors, mutations in the nuclear or mitochondria DNA or chromosomes anomalies. Around a third of all patients with epilepsy present a drug-refractory response, which is likely related to a genetic multifactorial feature. The up-regulation of drug transporters at the blood-brain barrier reduces anti-epileptic drugs accumulation favoring drug resistance in epilepsy treatment. Moreover, the complex trait of epilepsy and the anti-epileptic drugs response are also influenced by epigenetic, developmental, and environmental factors [8].

Epilepsy syndromes are frequently linked to metabolic abnormalities such as those related to mitochondrial metabolism, dysfunction in the regulation of essential metabolites, for example, folate, cholesterol, and amino acids. The identification of metabolic anomalies in patients with epilepsy may lead to a more efficient treatment and prognosis [5]. The epilepsy diagnosis syndrome can be a difficult medical task. The most used methods for diagnosing epilepsy today is electroencephalogram; complete blood count and chemistry panel are complimentary to the diagnosis. Regarding the treatment, it is based on seizure medications such as anticonvulsant, ketogenic Diet, nerve stimulation and surgery [7].

Polymorphisms in genes that code for neurotransmitters and neuropeptides may be involved in the pathophysiology of epilepsy as well. It has been shown that anomalies in glutamatergic and GABAergic synaptic transmission in the origin of the paroxysmal depolarization shifts is related to the onset of epileptic seizures. Several genes and their variants are under investigation whether they could affect the onset of epilepsy [9–13]. The brain-derived neurotrophic factor (BDNF) gene regulates processes related to brain development, synaptic activity, cognition and memory [9]. BDNF is target of studies regarding the gradual process by which a normal brain develops epilepsy [10]. Other factors are closely associated to the anti-epileptic drug resistance, such as the p-glycoprotein, a drug efflux transporter encoded by ATP-binding cassette subfamily B member 1 (ABCB1) [11], a highly polymorphic gene with more than 50 variants within the coding region. In addition, polymorphisms in N-acetyltransferase-2 (NAT2) [12] or thiopurine-S-methyltransferase (TPMT) [13] are well-investigated and they play a role in drug resistance in a variety of diseases, including neurological ones. The most common method for identifying genetic polymorphisms related to epilepsy is based on polymerase chain reaction (PCR) coupled with restriction fragment length polymorphism analysis and followed by gel electrophoresis [11].

Drug response is governed by interactions of several genes and environmental factors. CYP2C19 and CYP2C9 are polymorphic drug metabolizing enzymes also associated to drug response. Heterozygous CYP2C9 was down-regulated in Caucasians epileptic patients that do not respond to anti-epileptic drug treatment [14] . It has been suggested that CYP2C9 contribute to a lower risk of developing drug resistance in epileptic patients [15]. Another gene implicated in the epilepsy susceptibility is the gamma-aminobutyric acid A receptor (GABRG2) [16]. GABRG2 acts as an inhibitory neurotransmitter in the central nervous system and polymorphism within its sequence increases

susceptibility to idiopathic epilepsy [17].

Here, we explore the features of the multifactorial genetic basis of epilepsy and its resistance against anti-epileptic drugs. Polymorphisms in relevant genes related to epilepsy are highlighted in order to discuss possible risk factors for the disease and point out alternatives to improve prognosis, therapy and the quality of life of patients. To achieve this goal, the present review focuses on the role of genetic polymorphisms of the ABCB1, BDNF and CYP2C9 genes (Figure 1). The scientific literature databases PubMed, EMBASE, and Google Scholar were searched using keywords "epilepsy gene polymorphism" "ABCB1 and epilepsy" "BDNF and epilepsy" "CYP2C9 and epilepsy" "epilepsy and drug resistance".

Brain-Derived Neurotrophic Factor

BDNF is the most abundant neurotrophin in the brain. Neurotrophins induce the development and survival of neurons [18]. Polymorphism investigative studies have shown that DBNF and its receptor (tropomyosin related kinase type B) were up-regulated during the process of epileptogenesis [19] and it has been point as possible target of epilepsy intervention [20]. The most common BDNF genetic polymorphism is Val66Met, which has been associated with the pathogenesis of several nervous system and psychiatrical, disorders [21]. The Val66Met variant is characterized by the replacement of C to T in rs6265 leading to a change from the amino acid valine into methionine in the 66th residue of the BDNF protein. The presence of the Val66Met polymorphism and epilepsy risk were assessed by meta-nalysis and significant associations were found in the Asian population [22].

Ions transporter channels are thought to be involved in the pathophysiology of epilepsy [23]. The potassium-chloride transporter 2 (KCC2) promotes chloride efflux, hyperpolarization of neurons and release of GABA [23]. Patients with deficiency in KCC2 suffer from frequent and generalized seizures [24]. Moreover, RT-PCR samples from patients with anti-epileptic drug resistance showed downregulation of KCC2 transporters [25]. BDNF is related to the regulation of KCC2 expression and it has been shown that microinjections of BDNF increase KCC2 expression [26]. Finally, it has been reporter that the development of epilepsy is significantly attenuated by intrahippocampal delivery of BDNF,

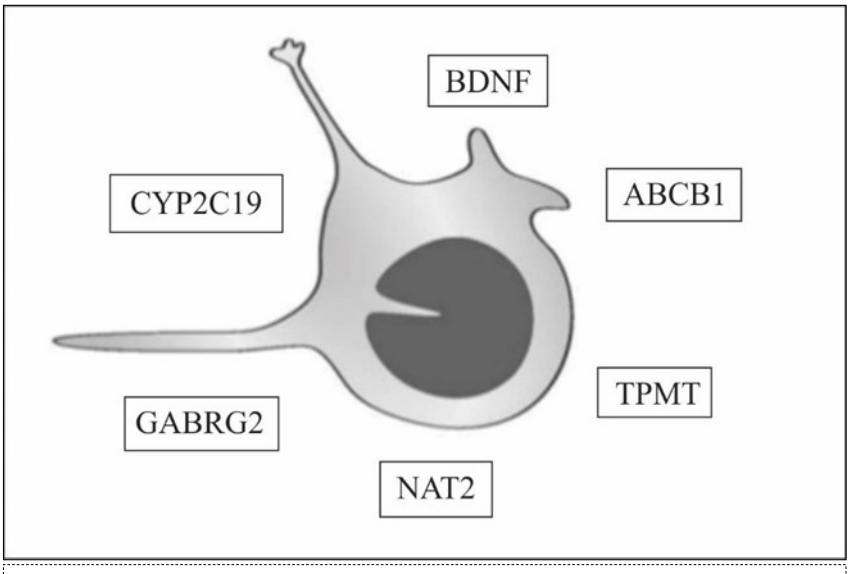

Figure 1. Schematic neuron highlighting the most important polymorphic genes related to epilepsy. All of these genes are targeted as possible biomarkers of epilepsy and of anti-epileptic drug resistance. DBNF (Brain-derived neurotrophic factor), ABCB1 (ATP-binding cassette subfamily B member), CYP2C19 (Cytochrome P450 2C9), TPMT (thiopurine-S-methyltransferase),GABRG2 (gamma-aminobutyric acid A receptor), NAT2 (N-acetyltransferase-2).

considered as a pro-epileptogenic factor [27,28]. Future studies need to be performed in order to evaluate the likelihood of therapeutic effects epilepsy through induction of endogenous BDNF.

ATP-Binding Cassette Subfamily B Member

Several single nucleotide polymorphisms in the drug-efflux transporter ABCB1 gene have been identified, such as, T129C and T1236C in exon 12, G2677T in exon 21 and C3435T in exon 27 [29–35]. Up-regulation of such transporters influence anti-epileptic drug resistance since their overexpression may impede drugs to reach their destination [11]. In addition, genetic polymorphisms in ABCB1 may account for the overexpression of drug-efflux transporters observed in patients with epilepsy [36].

P-glycoprotein is a fenobarbital transpoter, a common anti-epileptic drug [37]. The involvement of drug efflux variants and risk of epilepsy is controversial, since polymorphisms in ABCB1 gene are associated with response to anti-epileptic drugs in certain assays [30,38–40] but not in others [41–43]. A large-scale study on 8604 patients concluded that the ABCB1 C3435T polymorphism could be used as a genetic marker for drug resistance in epilepsy [44]. In fact, the C3435T variant is described as critical to anti-epileptic drug resistance [45].

Cytochrome P450

Cytochrome P450 2C9 (CYP2C9) takes part in the catalysis and metabolic clearance of many important drugs. CYP2C9 is the most common CYPs in the liver, accounting for the metabolization of 15% of all clinical drugs [46]. Genetic polymorphism in the CYP2C9 gene affect metabolization of drugs such as phenobarbital [47]. CYP2C9 is highly polymorphic, with more than 40 variants described in the literature. The most frequent polymorphisms of CYP2C9 are Arg144Cys (CYP2C9*2) and Ile358Leu (CYP2C9*3) and they show reduced catalytic activities [48]. CYP2C9 is involved in several metabolic processes and is responsible for the biosynthesis of endogenous reactive oxygen species [49]. It has been found that epileptic patients carrying the CYP2C9 polymorphism had lower total triglyceride and cholesterol levels due to induction of CYP2C9 [50]. In addition, biopsy assays have shown a positive correlation among serum lipid, hepatic enzyme activity and CYP450 levels in liver [51], mainly in epileptic patients undergoing phenytoin treatment.

The genetic variation of CYP2C9 reduce the metabolism of anti-epileptic drugs by 25–50% in patients [52]. Polymorphisms have a close relation to the variability in pharmacokinetics and pharmacodynamics of anti-epileptic affecting aspects such as efficacy, side effects, duration of action and resistance [53,54]. Several aspects influence the metabolization and occurrence of side effects associated anti-epileptic drugs, such as age, index mass, pregnancy and drug interactions, in addition to CYP2C9 and other genes gene polymorphisms [14]. The identification of polymorphisms needs to be optimized in order to be more cost-effective. Ideally, in the future we will focus on the determination of the metabolization rates and drug interactions prior to prescription and administration in order to establish a more personalized medicine in the treatment of epilepsy.

Concluding Remarks

Early identification of risk factors for epilepsy should optimize treatment and prognosis. The characterization of genetic polymorphism contribute to the selection of the most promising antiepileptic therapy and avoidance of drug resistance. The necessity of developing biomarkers to estimate the risk of inducing drug resistance is real once variation in drug metabolizing genes have a clinical impact on the anti-epileptic drug therapy.

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