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Systematic Review

Genomic and Personalized Medicine Perspective in Genetic Generalized Epilepsy

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Abstract

The genetic generalized epilepsies (GGEs) are a set of disorders presenting with generalized seizures, in addition to general spike-wave activity. The present study aims to investigate the clinical manifestations and genetic origin of generalized tonic-clonic seizures and the subgroups of GGEs, including childhood absence epilepsy (CAE), juvenile absence epilepsy, and juvenile myoclonic epilepsy (JME). Information compiled from genome-wide association studies (GWASs) in the EPICure project revealed associations with many genes. Besides, copy number variant (CNV) discoveries have been the most inspiring turning point of epilepsy genetic research. This phenomenon could give us an idea about microdeletions/microduplications as genetic variants throughout the whole genome. Nowadays, next-generation sequencing (NGS) approaches support neurogeneticists to unravel the predisposed putative variants in GGE to establish a better diagnosis. Consequently, previous experiments supply data for antiepileptic drugs (AEDs) to test susceptible variants, which influence the response to drugs. As a final point, all these data should provide the current GGE patients with better genetic counseling and follow-up services.

Keywords: AED, Antiepileptic drug, CNV, Copy number variant, Epilepsy, GWAS, Genome wide association

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Introduction

Genetic generalized epilepsy (GGE) is a definition for a category of epilepsy syndromes without any focal onset mechanism and an internal source, preferably with a genetic cause.[1] Based on acceptable clinical documents regarding the pathogenic variants involved in epilepsy patients, the GGEs are categorized as a type of idiopathic generalized epilepsies (IGEs). According to the International League Against Epilepsy (ILAE) classification, the GGE is classified into four accepted subcategories, including childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and generalized tonic-clonic seizures alone (GT-CSA).[2] There is also phenotypic overlap among GGE syndromes as depicted in Figure 1 in comparison with a genetic overlap in GGE subtypes.[3,4] In order to define the exact characteristics of each subcategory, they are described in detail in the following sections.

Childhood Absence Epilepsy

This form of GGE, also known as pyknolepsy, is distinguished by its onset time (mostly occurring at the age of 6 years) and characterized by seizures of unexpected onset interrupting constant activities and lasting from seconds to less than a minute (4–20 seconds) with a likely eye rotation.[5] The annual incidence of this condition is 2–8 cases per 100 000 children aged <16 years. Based on the statistics, CAE has a prevalence rate of 2%–10% among children with epilepsy. The CAE can be also discriminated by numerous daily distinctive absence seizures, which go along with bilateral, symmetrical, and synchronous 2.5–4-Hz spike-wave discharges and slow-wave discharge (SWD) presenting in the electroencephalogram.

This condition comprises about 5% of all childhood epilepsies.[3,6] The genetic origin of CAE is subdivided into two different categories based on the function of gamma-aminobutyric acid$_A$ (GABA) receptor ϒ2 subunit (*GABRG2*) and voltage-gated Ca^{2+} channel α1A subunit (*CACNA1A*). The *GABRG2* gene is associated with 5q31.1–33.1 (R43Q) and 5q31.1–33.1 (K289M). The impact of the mutation of the former locus protein is lack of benzodiazepine-mediated (BDZ) potentiation of GABA$_A$ receptor, resulting in no stimulation in GABA action. On the other hand, the latter locus induces no effect on the action of GABA but may affect BDZ-

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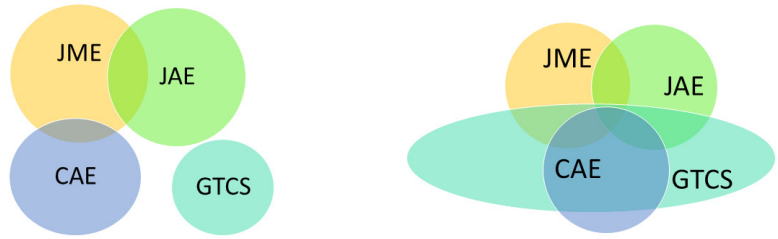

Figure 1. Genetic Overlapping (Left) Versus Phenotypic Overlapping (Right) In Genetic Generalized Epilepsies.

mediated potentiation of $GABA_A$ receptor.[7,8] Besides, *CACNA1A* gene is linked to 19p13.2–13.1 (R1820stop), and the effect is loss of the Ba^{2+} current.[9]

Juvenile Absence Epilepsy

Through many substantial overlaps with CAE, this type of manifestation occurs at the age of 10–12 years in a sporadic manner (usually less than once a day; i.e., non-pyknoleptic, NPA).[10,11] These absence seizures are associated with bilateral, symmetric, and synchronous states like CAE but with a discrepancy of 3–4 Hz SWD.[12,13] Mutations associated with this state occur in the *EFHC1* and *CLCN2* genes. The *EFHC1* gene is mapped to 6p12.2, which translates to EF-hand-containing calcium-binding protein that comprises calcium homeostasis. Additionally, *CLCN2* is linked to 3q27.1 and codes for a transmembrane protein that helps with the homeostasis of chloride ion in several cells.[14]

Juvenile Myoclonic Epilepsy

This kind of epilepsy is the most expected and distinct GGE.[15,16] The symptoms of this seizure present during the juvenile period. The JME is accompanied by a wide range of signs, including arrhythmic, uneven, and recurring myoclonic jerks, generally in the arms. These jerks are the probable causes of unexpected patient fall. No trouble of consciousness is obvious in JME. This form of GGE has an inherited pattern in some cases and is not gender-limited.[17] JME patients show normal intelligence; nevertheless, it should be noted that JME is linked to frontal lobe dysfunction. Studies are indicative of microdysgenesis in the category of cortical and subcortical dystopic neurons and further abnormalities in microscopic and structural forms.[18]

The *GABRA1*, *SCN1A,* and *EFHC1* genes are involved in JME. The *GABRA1* is mapped to 5q34 and is in charge of the function of GABA receptors that are ligand-gated chloride channels.[19] On the other hand, *SCN1A* is associated with 2q24.3 and accounts for voltage-dependent sodium channels, regulating sodium ion reciprocity in the intra- and extracellular spaces. These genes are vital for the production and proliferation of action potentials in two distinct groups of cells, namely those of the muscles and neurons.[20]

Generalized Tonic-Clonic Seizures Alone

The GT-CSA is defined by spike-wave discharges in a general type (2.5-5 Hz) involving the bilateral hemispheres during seizures.[21] The GT-CSA is linked to an augmented prospect of damages and sudden unexpected death in epilepsy.[22] It should be mentioned that GT-CSA happens in 30–60% of children with CAE.[23] The GT-CSA involves a similar deep loss of consciousness. The epileptic events are formed by an extensive and identical process inside the cerebral cortex.[24] The *CERS1* gene is linked to 19p13.11 and is in charge of ceramide synthase enzyme, which catalyzes the synthesis of ceramide (i.e., hydrophobic moiety of sphingolipids). The encoded enzyme synthesizes 18-carbon ceramide in the brain neurons (Table 1).[25]

Genome-wide Association Studies as a Major Genome-scale Approach in Genetic Generalized Epilepsies Investigations

Genome-wide association studies (GWASs) have revolutionized genomic medicine through the

Table 1. Genetic Classification of Genetic Generalized Epilepsies Based on Main Known Genes

Condition	Implicated Gene(s)	OMIM Accession Number	Chromosomal Location	Gene Function
Childhood absence epilepsy	*GABRG2*	*137164	5q34	$GABA_A$ receptor ϒ2 subunit
	CACNA1A	*601011	19p13.13	Voltage-gated Ca^{2+} channel α1A subunit
Juvenile absence epilepsy	*EFHC1*	*608815	6p12.2	EF-hand-containing calcium binding protein
	CLCN2	*600570	3q27.1	Chloride ion transmembrane protein
Juvenile Myoclonic Epilepsy	*GABRA1*	*137160	5q34	GABA receptor
	SCN1A	*182389	2q24.3	Voltage-dependent sodium channels
	EFHC1	*608815	6p12.2	EF-hand-containing calcium binding protein
Generalized tonic-clonic seizures alone	CERS1	*606919	19p13.11	Ceramide synthase enzyme

identification of susceptibility genes involved in complex human diseases, such as GGEs. Such investigations have facilitated the identification of robust associations between thousands of single-nucleotide polymorphism (SNP) markers and different kinds of diseases in a large population. The GGE is renowned as one of the most common forms of epilepsy.[26]

The genome-wide investigations commonly detect the association between common variants like SNPs and common diseases. These studies are unbiased and apply extremely stringent criteria based on statistical significance.[27] Although the act of sporadic variants is not enclosed by conventional genome-wide genotyping arrays, they may signify a central and pivotal element of complex trait genetics because it is assumed that they have a larger effect on phenotype. Contrary to the common-variant GWASs, there are countless dissimilar forms of surveys and analytical methods that can be employed in the association studies with an emphasis on exploring rare variants. In this regard, burden and kernel tests are used in this method.[28] Moreover, recent developments in next-generation sequencing (NGS) technologies have resulted in substantial progress, enabling the analysis of rare variants discussed in GWAS; accordingly, it has exerted a reasonably huge impact on common diseases like epilepsy.[29]

In a comprehensive study mainly performed by EPICure Consortium researchers in Europe in 2012, a GWAS was carried out on GGE and susceptibility loci at 1q43, 2p16.1, 2q22.3, and 17q21.32. The study included 3000 patients with GGE and 4000 controls. The linked regions employ top candidate genes, including *ZEB2* at 2q22.3, *PNPO* at 17q21.32, *HRM3* at 1q43, *SCN1A* at 2q24.3, and *VRK2* at 2p16.1. The mentioned two-stage GWAS included 3020 patients with GGEs and 3954 controls with European ancestors.[30] The most significant locus in relation with GGEs discovered in the EPICure study was 2p16.1 harboring *VRK2* and *FANCL*.

The *FANCL* gene (Fanconi anemia complementation group L) and *VRK2* (a serine-threonine kinase) were associated with both epilepsy and schizophrenia.[31] The EPICure GWAS also identified an intergenic variant in the proximity of *SCN1A* gene as a common risk factor that is regarded as the prime candidate gene for a wide range of epilepsies. Region 2q24.3 harbors an SNP called *rs11890028* with a *P* value of 4.0×10^{-6} and is nearby the *SCN1A* gene. Based on GWAS, this region is one of the most important variants (40%) in epilepsy patients.

In addition to the mentioned region, there are also other variants in *SCN1A* gene causing Dravet syndrome and generalized epilepsy with febrile seizures. According to the authors of the mentioned article, additional works are required to explicate whether these positional candidate genes donate to the heritability of the common GGE syndromes or not. More detailed information about this study can be seen in Table 2.[30]

Another large study was performed by the ILAE consortium in 2014. It was a meta-analysis including 9000 patients and 26 000 controls to explore the common genetic variants inducing a high risk of epilepsy, such as the IGE/GGEs and focal epilepsies. The mentioned meta-analysis contained evidence regarding *VRK/FANCL*. This finding originates from the EPICure GGE GWAS, which contributes to the mainstream of GGE patients. The mentioned study, as a broad meta-analysis, has shed light on previous association studies in epilepsy and highlighted the act of *SCN1* mutations in GGEs.[32]

Copy Number Variants as the Main Turning Point in Epilepsy Genomics Studies

Copy number variants (CNVs) are structural genomic variations in an entire chromosome within a range of 1 kb that suggestively contribute to the genetic architecture of several neurogenetic and neurodevelopmental disorders. The CNVs include both normal and pathogenic variants throughout the genome. If one divides epilepsy molecular genetic investigations into two major periods, including pre-genomic era and genomic era, researches are predominantly dealing with GGEs, and the introduction of CNVs was truly a major turning point in this domain. Regularly, rare CNVs contribute to 5%–10% of patients with childhood epilepsies.[33]

Two core categories of CNVs are recurrent and non-recurrent types. The recurrent version can present by repeated CNVs with deletions and duplications that occur

Table 2. Genome-Wide Association Studies of Variants

Variant (SNP)	Functional Class	*P* Value	Odds Ratio	Chromosomal Location	Reported Gene(s)
rs13026414-C	Intergenic variant	2×10^{-9} (All GGE)	1.23	2p16.1	Intergenic
rs72823592-G	Non-coding transcript exon variant	9×10^{-9} (All GGE	1.3	17q21.32	*SNX11, SKAP, CDK5RAP3, PNPO, ATAD4, COPZ2, hsa-mir-152, NFE2L1, CBX1*
rs10496964-C	Intergenic variant	9×10^{-9} (GAE)	1.47	2q22.3	*ZEB2*
rs12059546-G	Intron variant	4×10^{-8} (JME)	1.42	1q43	*CHRM3*
rs39861-C	Intron variant	3×10^{-7} (JME)	1.26	5q12.3	*MAST4*

The GWAS catalog of IGEs/GGEs performed by EPICure consortium study (2012)

The initial sample description includes 702 genetic absence epilepsy cases, 586 juvenile myoclonic epilepsy cases, 239 cases of other genetic generalized epilepsies, and 2461 controls, all originating from European ancestry. The main sub-populations were patients with genetic absence epilepsy and juvenile myoclonic epilepsy. The main platform and the single-nucleotide polymorphism passing QCs was Affymetrix [4560000].

as a result of non-allelic homologous recombination in the meiosis. They are regarded as aberrant recombinations. This type of CNV is principally restricted to the known hotspot deletions.[34] On the other hand, non-recurrent CNVs arise from the genomes, which are primarily due to replication molecular errors; however, such breakpoints are not constant.

Non-recurrent CNVs are frequently unique and rare.[35] The exploration of CNVs on the genomic scale became actually feasible with an overview of array comparative genomic hybridization and SNP genotyping arrays. These advances have facilitated a reliable assessment of rare CNVs that are too small to be observed by conventional cytogenetic methods.[36] In addition to epilepsy, the major known CNVs are considered common etiological factors, which play an important role in the vast majority of neuropsychiatric disorders, including schizophrenia, intellectual disability, and autism.[37]

One of the first projects in which the CNVs were investigated among GGE patients was performed by Kovel et al They discovered that frequent microdeletions at 15q13.3, 15q11.2, and 16p13.11 may be also involved in epileptogenesis; therefore, they can be the main predisposing factors for GGEs. In addition to GGEs, they found that these putative recurrent microdeletions have a wide susceptibility impact on numerous neuropsychiatric disorders.[38] In another study, 15q13.3 microdeletion was reported to have the most significant risk in GGE with an odds ratio of 68.[39] On the other hand, the results of an investigation performed by Heinzen et al showed that 15q11.2 and 16p13.11 microdeletions also exist in patients with focal epilepsies and some other types like epileptic encephalopathies.[40]

In addition to the mentioned microdeletions, which have been discovered by advanced technologies, the rare deletions in the coding area of some neuronal genes have been recently shown to play a significant role in epileptogenesis in GGE patients. For example, a study carried out by Moller et al demonstrated that the deletions of *NRXN1* in the form of exon-disruptive, as an adhesion molecule in neurons placed in the presynaptic terminal, can increase the risk of GGE.[41] Furthermore, the exonic deletion of another neuronal gene, namely *RBFOX1*, which codes a neuron-specific RNA-binding protein, reportedly increases the risk of GGE.[42]

The results of a leading study performed by Lal et al in the frame of a comprehensive genome-wide burden analysis revealed that the expressively increased liability of microdeletions in GGE patients is principally restrained to regular hotspot microdeletions. These microdeletions lead to the disruption of neurodevelopmental genes, thereby inducing a strong impact on the development of the nervous system and its role in the pathogenicity of common GGE syndromes.[43]

Molecular Diagnostics and Genetic Counseling Issues in Genetic Generalized Epilepsies

Epilepsy is a neurological disorder including such hallmarks as the sudden frequent events of sensory disturbance and lack of consciousness due to abnormal electrical actions in the brain. This disorder is a relatively frequent disease affecting 1% of the people around the world at different age groups in a wide range of types with diverse manifestations.[44] In the last decade, the genetics of epilepsy witnessed a revolution. In this regard, the current knowledge about the causative genetic variants has improved by developing NGS technologies, including targeted gene panels, whole exome sequencing, and whole genome sequencing.[45]

Epilepsy is caused by a number of genes consisting of common and rare genomic variants with different effect sizes.[44,45] The IGE/GGEs, constituting a significant proportion of common epilepsies owing to the implication of genetic factors, do not have a definite cause. These seizure disorders, such as CAE, GT-CSA, and JME, are genetically heterogeneous.[45] They are practical targeted gene panels for the detection of mutation in heterogeneous disorders, such as cardiomyopathies, neuromuscular diseases, retinopathies, and epilepsy.[46]

For the sake of clinical diagnosis, despite the fact that the monogenic causes of epilepsies have been under major focus in this field, the clinical significance of several common and rare variants remains uncertain. Given the high heterogeneity of genetic architecture, the investigation of the causative genetic variants through NGS techniques has been unsuccessful so far.[45] Therefore, the adoption of diagnostic panels through simultaneous targeted sequencing of a number of causative genes and the replacement of Sanger sequencing with a massively parallel sequencing have led to appropriate therapeutic recommendations (for a few genes).[44] Low coverage of a base-pair position and improvement of enrichment procedures for the sequencing of the target are the two chief issues determining the sequence quality.[46]

The current commercial panels available for the diagnosis of epilepsy are able to evaluate about 400 genes (CeGaT GmbH, Tübingen, Germany). The panels with a flexible design and the capability of covering a large number of genes (in a spectrum of 11 to 455 genes) are proper for diagnostic purposes. Even though GGEs are rarely monogenic, the total molecular harvest of NGS technologies in all of the studied cases will only reach up to 20%–30%.[44,47,48]

As mentioned above, given the high heterogeneity of GGEs, genetic counseling and its subsequent clinical assessments face some difficulties. In severe epilepsies, the major mechanism of pathogenicity appears to be monogenic inheritance, such as *de novo* mutations (while unaffected parents do not carry the causative variant, their affected offspring do) and recessive mutations. However,

GGEs are mainly assumed to be caused by complex genetic disorders for which a few genetic risk factors have been identified up to now.[45]

One of the helpful measures in the genetic counseling of GGE patients and their relatives with a possibly decreased recurrence risk is identification of the genetic background of an epileptic phenotype. This measure would lead to establishment of appropriate clinical diagnosis, thereby eliminating the need for implementation of an infinite series of difficult, demanding, and costly diagnostic trials. Moreover, it facilitates the prediction of the future progression of this disorder or even the development of antiepileptic medicines.[46]

In addition, detection of mutation in well-known causative genes in patients with epilepsy plus an infrequent or general presentation of a seizure disorder can support the genetic counselor to diagnose the accurate phenotypic range of the disorder. In case the phenotype of the epilepsy is unspecific, establishment of a definite clinical diagnosis will be a challenging task to the genetic counselor. However, the specificity of the supplementary elements, including associated disorders, positive family history, laboratory criteria, dysmorphisms, or malformations, can contribute to making a proper clinical diagnosis.[46]

One of the complicated aspects of screening for mutations in underlying genetic defects is the multitude of putatively responsible genes, each of which has a low individual prevalence and mutation detection rate.[46] In many cases with sporadic developmental disorders, particularly early-onset epilepsies in a severe form, which are theoretically recessive in nature, the rising indication provided by NGS indicates that they originate from dominant genes in *de novo* form . These findings are of special importance in genetic counseling and prenatal diagnostic trials.[47]

While the genes involved in inheriting epilepsy account for a minority of cases, the number of the recently discovered genes associated with monogenic epilepsies has risen to more than 150 genes. As a result, only individuals managed with NGS techniques can benefit from pharmaceutical treatment.[47,49,50]

The JME is more prevalent in females; however, the offspring of an affected father have a five-fold subordinate risk of epilepsy compared to the offspring of an affected mother. While the recurrence risk for the first-degree relatives of a patient is about 5%–8%, this risk for the second-degree relatives and the offspring has been reported at 5% and 8%–12%, respectively. Regarding the GT-CSA patients who specifically have absence seizures, the first-degree relatives have an extremely increased risk of recurrence.[51,52]

Pharmacogenomics of Anti-epileptic Drugs

A number of pharmacological agents used in the treatment of epileptic seizures are recognized as antiepileptic drugs (AEDs), which are also called anti-seizure drugs or anticonvulsants.[53,54] The AEDs do not equally affect all GGE patients; however, the reason for this has remained uncertain yet.[55] Some of the AEDs exhibit anti-epileptogenic effects that prevent the development of epilepsy, halt, or reverse the progression of this disease in animal models. Nonetheless, there are no available data and clinical trials proving the exact antiepileptogenic effect of AEDs in humans.[56,57]

There are different classes of AEDs commercially available.[58] The conventional AEDs are presumably able to inhibit sodium channels or boost the function of GABA.[59] Although the mechanism of AEDs actions is unclear, based on the evidence, the AEDs are proposed to act via reducing excitatory glutamate release (which is raised in epilepsy) through blocking actions. Moreover, the additional targets of AEDs are $GABA_A$ receptors, GABA transaminase, voltage-gated calcium channels, GAT-1 GABA transporter, SV2A, and α2δ.[59,60]

Based on the guidelines presented in the American Academy of Neurology and American Epilepsy Society, newly diagnosed epilepsy patients who are in demand of treatment can initiate their treatment with standard AEDs (e.g., carbamazepine, phenytoin, valproic acid/valproate semisodium, and phenobarbital) or novel AEDs (e.g., gabapentin, lamotrigine, oxcarbazepine, and topiramate), which are prescribed based on the patient's individual characteristics. Among the common AEDs, levetiracetam is used for JME patients. The response of GGE patients to treatment is about 80%, and it seems that they are entirely under control.[61,62] This may indicate the promising perspective of AEDs-based treatment for patients suffering from GGEs.

Variations across the causative genes of epilepsy can affect both pharmacokinetics and pharmacodynamics, thereby leading to variable drug responses in different patients.[63] The intervening mechanisms, such as pharmacokinetics and pharmacodynamics, occurring as a result of gene polymorphisms influence the function of enzymes, receptors, and ion channels, and consequently modify the AED targets. Likewise, a mutation in epilepsy-related genes can immensely influence the reaction to AEDs.[63-65]

As for pharmacokinetics and pharmacodynamics, the evidence is indicative of the effect of the allelic variant of polymorphic *CYP2C9* and *CYP2C19* genes, leading to significant differences in the concentration of AEDs in the serum. The *CYP2C9* metabolizes 90% of phenytoin, and polymorphisms are considered as the major determinants of phenytoin metabolism rate. Phenytoin metabolization at a slower rate would occur in the presence of *CYP2C9*2* (*rs1799853*) and *CYP2C9*3* (*rs1057910(C)*) variants of *CYP2C* gene. This would be followed by a significant increase in neurotoxicity based on concentration.[63,66,67]

Based on a recognized sign in *CYP2C19* gene, there is an association between serum concentration and the clinical efficacy of clobazam owing to the gene-dose effect.[63,68,69]

According to the evidence, the polymorphisms of a number of genes, namely *UGT2B7, SCN1A,* and *ABCC2,* display an association with oxcarbazepine preservation in patients with epilepsy in Han Chinese population.[63,70] In addition, *CYP1A1* variant *rs2606345* accounting for decreased expression of *CYP1A1* gene was reportedly associated with poor response to the first-line AEDs in an Indian female epilepsy patient.[63,71,72] Despite the fact that the link between *ABCB1* genetic variants and response to treatment in epilepsy has been demonstrated in many studies, this relationship is not conclusive yet.[63,73-75] Recent studies have shown that the drug response would be specified to the location of mutations in *SCN1A* gene.[63,76,77]

In many rare cases of GGEs, genetic profiles can lead to treatment stratification. This occurs whenever the genetic testing is performed for casual mutation. For instance, *SCN1A* mutations are observed in patients suffering from Dravet syndrome. Approximately 50% of patients show a negative reaction to AED drugs. Immunologic hypersensitivity to AED therapy (e.g., toxic epidermal necrolysis) is one of the most severe adverse drug reactions, which is linked to genetic polymorphisms in the human leucocyte antigen (HLA) complex. Implementation of some pharmacogenetic screening in Asian populations for HLA-B*15:02 can facilitate the prevention of Stevens-Johnson syndrome which is caused by carbamazepine.

Moreover, HLA-A*31:01 is known as a potential risk marker for all phenotypes of carbamazepine-induced hypersensitivity with applicability in European and other populations.[65] Beside treatment stratification and pharmacogenetic screening, the genetic profiling of GGE patients could have significant outcomes, even in surgical treatments. For instance, in a study performed in 2015, Skjei et al questioned the benefit of cortical resection in epileptic children with *SCN1* mutations. Their findings suggested a diffuse pathophysiological mechanism of the patients' epilepsy which will not respond to focal resective surgeries.[78]

Epilepsy is a complicated form, and an assortment of genetic bases accounts for its various types. Considering this, it is expected that the clinical responses of the subjects participating in this study are different from those of other populations around the world. Interventions will be determined according to the patient's genetic basis. Table 3 summarizes 11 trials addressing the genetic diversity of individuals and their subsequent pharmacological effects. After multiple trials in various populations, the drug responses should be identified and adopted in clinical settings.

Future Studies

New technologies are playing a chief role in establishing a proper genetic diagnosis and achievement of functional findings regarding the previously and newly discovered variants in epilepsy. Likewise, these advances have helped the geneticists and clinicians to suggest modern treatments for patients suffering from different types of epilepsy. The directions for handling epilepsy patients include chromosomal microarray, gene panel, and single gene analysis, regardless of identification of a particular phenotype.

Subsequent to clinical guidance, novel findings are expected to be discovered owing to the vast spectra of epilepsy and large experiments conducted hereafter. In recent years, whole exome sequencing has emerged as a practical approach to unravel new variants involved in the pathogenicity of epilepsy. This approach has also prepared a large dataset for evaluating the importance of variants. Novel variants are going to be investigated through CRISPR and iPSC technology, which are devised to provide precision medicine data. Exploration of modern technologies has led to the popularization of individualized medicine and relief of the families who are abiding epilepsy and looking for disease causes and new treatments.[79]

Authors' Contribution

PT and MD introduced the project and wrote the main body of the article. DMR, SP, and HA helped in data collection. MHA managed the project.

Conflict of Interest Disclosures

The authors declare no conflict of interest..

Ethical Statement

Not applicable.

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Table 3. Reviewed Clinical Trials Addressing Genetic Generalized Epilepsy

NCT Number	Title	Recruitment	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
NCT0091690	Genetic Disease Gene Identification	Unknown status	IGE, etc.	N.A.	Study type: Observational/family-based Outcome measures: Identification of gene/mutation responsible for disorder	Enrollment: 200 Age: 6 month and older (children, adults, and seniors) Gender: All	State University of New York, Upstate Medical University	2005-2009	SUNY Upstate Medical University, Syracuse, New York, United States (U.S.)
NCT0185828	Genetics of Severe Early Onset Epilepsies	Recruiting	Epileptic encephalopathy, Ohtahara syndrome, Dravet syndrome, etc.	N.A.	Study type: Observational/ cross-sectional Outcome measures: Identification of new or existing causative mutations through whole exome sequencing of epilepsy patients	Enrollment: 500 Age: children, adults, and seniors Gender: All	Boston Children's Hospital Dravet Syndrome Foundation	2010-2017	Boston Children's Hospital, Boston, Massachusetts, U.S.
NCT0172378	Genetic Studies in Patients and Families with Infantile Spasms	Active, not recruiting	Infantile spasms	N.A.	Study type: Observational/family-based Outcome measures: Determination of the effectiveness of novel genetic analyses in suggesting disease-modifying genes	Enrollment: 63 Age: 31 days to 21 years (children and adults) Gender: All	University of Colorado, Denver	2013-2017	Children's Hospital Colorado, Aurora, Colorado, U.S.
NCT0055204	Epilepsy Phenome/ Genome Project (EPGP)	Unknown status	Lennox-Gaustad syndrome, localization-related epilepsy, infantile spasms, etc.	N.A.	Study type: Observational/case-control Outcome measures: EPGP will recruit persons with specific forms of epilepsy. DNA will be isolated from participants' blood, and genetic variants associated with common forms of epilepsy will be identified	Enrollment: 4150 Age: Up to 60 years (children and adults) Gender: All	University of California, San Francisco NINDS	2007-2014	University of Alabama at Birmingham, Epilepsy Center, Birmingham, Alabama, U.S. •Mayo Clinic College of Medicine, Phoenix, Arizona, U.S. •University of California, San Francisco, California, U.S. •The Children's Hospital, Denver, Colorado, U.S. •Johns Hopkins University, Baltimore, Maryland, U.S. •Children's Hospital Boston, Massachusetts, U.S., etc.
NCT0288538	Molecular Genetics in Infantile Spasms	Completed	Infantile spasms West syndrome	N.A.	Study type: Observational/case only	Enrollment: 41 Age: 3 months to 15 years (children) Gender: All	Hospices Civils de Lyon	2010-2016	

Table 3. Continued

NCT Number	Title	Recruitment	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
NCT0051871	Clobazam in Patients with Lennox-Gaustad Syndrome	Completed	Epilepsy, generalized	•Drug: clobazam at a low dose •Drug: clobazam at a medium dose •Drug: clobazam at a high dose •Drug: placebo	Study type: Interventional/ three-phase Outcome measures: •Percent of the decrease in the number of drop seizures (12-week maintenance period). •Percent of the decrease in the number of drop seizures (first 4 weeks of the 12-week maintenance period). •Percent of the decrease in number of drop seizures (middle 4 weeks of the 12-week maintenance period). •Percent of the decrease in the number of drop seizures (last 4 weeks of the 12-week maintenance period). •Percent of patients considered treatment responders defined as those with a ≥25%, ≥50%, ≥75%, 100% decrease in drop seizures (12-week maintenance)	Enrollment: 238 Age: 2 years to 60 years (children and adults) Gender: All	Lundbeck LLC, Industry	2007-2012	•University of Alabama at Birmingham, Huntsville, Alabama, U.S. •St. Joseph's Hospital and Medical Center, Phoenix, Arizona, U.S. •Phoenix Children's Hospital, Phoenix, Arizona, U.S. •Children's Hospital Los Angeles, Los Angeles, California, U.S. •The Children's Hospital, Aurora, Colorado, U.S. •Children's National Medical Center, Washington, District of Columbia, U.S. •Pediatric Neurology and Epilepsy Center, Loxahatchee, Florida, U.S. •Child Neurology Center of NW FL, Pensacola, Florida, U.S. •The University of South Florida, Tampa, Florida, U.S. •Pediatric Epilepsy & Neurology Specialists, Tampa, Florida, United States •and 43 more
NCT0016298	Clobazam in Patients with Lennox-Gaustad Syndrome	Completed	Epilepsy, generalized	•Drug: Clobazam at a low dose •Drug: clobazam at a high dose	Study type: Interventional/ two -phase Outcome measures: •Percent of the decrease in the number of drop seizures. •Comparison of the high-dose group with low-dose group regarding the percent of the decrease in the number of drop seizures. •Percent of patients considered treatment responders defined as those with ≥ 25%, ≥ 50%, ≥ 75%, and 100% reduction in drop seizures. •Parent/caregiver global evaluations of the patient's overall change in symptoms.	Enrollment:68 Age: 2 years to 30 years (children and adults) Gender: All	Lundbeck LLC, Industry	2005-2012	•Barrow Neurological Institute, Phoenix, Arizona, U.S. •Children's Hospital Los Angeles, Los Angeles, California, U.S. •Children's National Medical Center, Washington, District of Columbia, U.S., etc.
NCT0004195	Search for Genes Influencing Childhood Absence Epilepsy (CAE) Study	Completed	CAE	N.A.	Study type: Observational/case-control Outcome measures: Saliva Sample	Enrollment: 185 Age: 3 years and older (children, adults, and seniors) Gender: All	Icahn School of Medicine at Mount Sinai NINDS	1998-2016	•Icahn School of Medicine at Mount Sinai, New York, New York, United States

Table 3. Continued

NCT Number	Title	Recruitment	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
NCT011080	Trial of Lithium Carbonate for Treatment of Osteoporosis-pseudoglioma Syndrome	Completed	Osteoporosis-pseudoglioma syndrome	Drug: lithium	Study type: Interventional/non-randomized Outcome measures: •pQCT of forearm and lower leg •Fracture	Enrollment: 5 Age: 4 years to 64 years (children and adults) Gender: All	University of Maryland	2010-2015	University of Maryland Amish Research Clinic, Lancaster, Pennsylvania, U.S.
NCT0161417	Growth Hormone for Osteoporosis-Pseudoglioma Syndrome	Withdrawn	Osteoporosis-pseudoglioma syndrome	Biological: human recombinant growth hormone	Study type: Interventional/singles-group assessment Outcome measures: •Bone quality by pQCT •Body fat percent	Enrollment: 0 Age: 4 years to 64 years (children and adults) Gender: All	•University of Maryland •Children's Hospital of Philadelphia	2013-2017	University of Maryland Amish Research Clinic, Lancaster, Pennsylvania, U.S.
NCT0029734	A study of the safety of topiramate given in combination with other medications in adults and children with seizures	Completed	Seizures epilepsy	Drug: topiramate	Study type: Observational Outcome measures: •Evaluation of the safety of oral topiramate as adjuvant therapy for focal epilepsy, Lennox Gastaut syndrome epileptic seizures and the generalized tonic-clonic seizures in adults and children aged 2 years and older. •Safety and tolerability evaluation will be performed by reporting AEs and clinical lab findings. •Evaluation of efficacy will be performed with the aid of descriptive statistics. •Overall assessments of the improvement in the seriousness of seizures will be performed.	Enrollment: 153 Age: 2 years and older (children, adults, and seniors) Gender: All	Janssen Cilag Pharmaceutica S.A.C.I., Greece, Industry	2003-2010	

Abbreviations: NINDS, National Institute of Neurological Disorders and Stroke; CAE, childhood absence epilepsy.

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