

REVIEW

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The influence of genetics on epilepsy syndromes in infancy and childhood

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Abstract

Genetics is rapidly evolving and is actively playing a role in how we diagnose and manage epilepsy. The definition of an epilepsy syndrome has changed throughout the years. The International League Against Epilepsy (ILAE) has developed a classification of the epilepsies and has recently described specific epilepsy syndromes taking into account emerging genetic information which is rapidly evolving as well as etiology-specific syndromes. Understanding genetics can help clarify the syndrome and its treatment. This review provides a history of the definition of a syndrome, and the evolving contribution of genetic information that is part of the syndromic classification. We provide few examples of several phenotypes/genotypes of epilepsy syndromes in infancy and childhood and treatment issues that may arise from the available genetic information. Epilepsy syndromes and their genetics have been rapidly changing as new gene technologies are being developed. Understanding genetics can help clarify the syndrome, its treatment, and will help change the field of epilepsy to improve patients quality of life by creating new means of preventing, controlling, and curing epilepsy.

Keywords: Syndrome, Epilepsy syndrome, Genetics, History of epilepsy genetics, ILAE history

Background

What is a syndrome?

The word “syndrome” is derived from a Greek word meaning “concurrence.” According to the Merriam-Webster Dictionary, a syndrome is defined as “a group of signs and symptoms that occur together and characterize a particular abnormality or condition” [1]. Epilepsy syndromes have evolved in understanding and definition over time. Grinker [2] stated that an epilepsy syndrome is “not only paroxysms accompanied by sensory or psychic disturbances ... (it) may be symptomatic of a variety of pathologic disorders within and outside the nervous system ... Such a vaguely definable group of conditions, produced by a diversity of possible causes, cannot be termed a disease”. Sorel defined a syndrome as “a group of several

regularly related symptoms; this grouping permitting diagnosis” Gastaut [3] added specific electroencephalographic patterns as part of a syndromic constellation and thus described several relatively specific epilepsy syndromes based on clinical and electroencephalographic patterns. Syndromes typically present within a specific age and remit at a certain time [4]. The initial list of syndromes using these criteria included photoparoxysmal epilepsy, startle epilepsy, hemiconvulsive-hemiplegia epilepsy, and benign occipital epilepsy of childhood [5, 6].

Main text

The International League against Epilepsy (ILAE) developed a classification system of seizures in 1981, a revised proposal in 1985, and then a classification of the epilepsies and epileptic syndromes in 1989 [7]. The 1989 report used the terms “syndromes” and “epilepsies” almost interchangeably. The 1989 Commission proposed that an epileptic syndrome is “an epileptic disorder characterized by a cluster of signs and symptoms customarily occurring together; these included such items as type of seizure,

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etiology, anatomy, precipitating factors, age of onset, severity, chronicity, diurnal, and circadian cycling and sometimes prognosis. However, in contradistinction to a disease, a syndrome does not necessarily have a common etiology and prognosis." [7]. These signs and symptoms may be clinical while ancillary studies may be helpful, and the electroencephalogram (EEG) may show certain characteristic abnormalities in a specific syndrome. Idiopathic epilepsies are defined by "age-related onset, clinical and electroencephalographic characteristics, and a presumed genetic etiology".

Indeed, the EEG and head magnetic resonance imaging (MRI) have been the two important ancillary tools used in determining a syndromic diagnosis and its possible etiology, as specific syndrome may be associated with various etiologies [8, 9]. In 2001, an ILAE Task Force on Classification and Terminology proposed a diagnostic scheme that included a syndrome as one of its axes; the syndromes that were included were from a list of 'accepted' epilepsy syndromes based on various publications. The definition of a syndrome was abbreviated as a "complex of signs and symptoms that define a unique epileptic condition. This could have involved more than just a seizure type: thus frontal lobe seizures per se, for instance, do not constitute a syndrome" [10]. In 2006, a revised catalogue of epileptic syndromes was compiled [11]. However, the syndromes included were not examined for validity and acceptance by the community.

The ILAE has revised the classification of the epilepsies and now it is organized based on three levels: seizure types, diagnosis of the epilepsy type, and epilepsy syndrome [12, 13]. This classification emphasizes the importance of establishing the etiology at each of the three levels. The epilepsy syndromes take into account disorders and diseases with diverse etiologies, and the etiology is considered at each level. These approaches demonstrate the importance of etiology and gene testing to the diagnosis of an epilepsy syndrome.

Epilepsy syndromes were listed in the Berg et al. proposal on the organization of seizures and epilepsies [14]. The authors discussed electroclinical syndromes, constellations, structural/metabolic epilepsies, and epilepsies of unknown cause but did not distinguish between disease and syndrome. The term "syndrome" was to be "restricted to a group of clinical entities reliably identified by a cluster of electroclinical characteristics." An example was provided as to how 'specific' syndromes can be classified by the age of onset. This paper was monumental in that it began to address among the contribution of emerging genetic information for the etiologies of syndromes. The term "constellation" was used for "entities that were not exactly electroclinical syndromes ... (but) were diagnostically meaningful forms of epilepsy

and may have implications for clinical treatment." This paper included a "Table 3" that suggested as an example that 'published or proposed' syndromes could be listed according to the age of onset or as a distinctive constellation of symptoms. However, this list again was not vetted to indicate that the included syndromes were the officially ILAE designated ones.

In 2017, the ILAE defined an epilepsy syndrome as a "cluster of features incorporating seizure types, EEG, imaging features, and genetic data (when available) that tend to occur together. It often has age-dependent features such as age at onset and remission, seizure triggers, diurnal variation, and sometimes prognostic implications [13]." It is stated that there is no one-to-one correlation with an etiologic diagnosis (as more than one diagnosis can overlap), but it can aid in guiding management. The current Nosology Task Force of the ILAE created in 2018 has now defined neonatal, infantile, childhood, and variable age epilepsy syndromes as well as the idiopathic generalized epilepsy syndromes recognized as distinct electroclinical entities [15–18]. A syndrome is now defined as a cluster of features: (seizure type(s), EEG findings, imaging findings, age-dependent features, triggers and sometimes prognosis) that occur together. A syndrome diagnosis provides more sophisticated information than does an epilepsy type diagnosis for some patients and carries prognostic and treatment implications. The Nosology Taskforce addressed the validity and clinical aspects of the syndromes, defined etiology-specific syndromes.

Following the 2017 Epilepsy Classification, the syndromes in each age group were subdivided into generalized, focal or generalized and focal, based on seizure type(s).

The Task Force created a distinct category for syndromes with developmental and/or epileptic encephalopathy (DEE) or syndromes with progressive neurological deterioration. The Task Force emphasized the genetic contributions to the causality of the syndrome. It also combined some previously considered separate entities and renamed some of the previously known epilepsy syndromes such as Ohtahara syndrome and early myoclonic encephalopathy to early infantile developmental and epileptic encephalopathy (EIDEE) as well as benign Rolandic epilepsy or benign epilepsy with centrotemporal spikes (SeLECTS) and Doose syndrome to epilepsy with myoclonic atonic seizures (EMAtS). The epilepsy syndromes have been divided into self-limited focal epilepsies, generalized epilepsies, and developmental and/or epileptic encephalopathies (DE and/or DEE). DE and DEE can have both focal and generalized seizures. The syndromes in which epilepsy is the main syndrome has been

described by the ILAE [15–18]. The epileptic encephalopathies (EE) are the group of diseases in which there is typically a regression and the epileptic activity itself is the etiology for the severe cognitive and behavioral impairments. A developmental encephalopathy (DE) refers to the developmental impairment without epileptiform activity. This can be seen in a child with an intellectual disability but no epileptiform discharges [4]. The 2017 classification of the epilepsies proposed the term DEE to describe an epilepsy with developmental impairment that can be due to both the underlying etiology (developmental encephalopathy) and superimposed epileptic activity (epileptic encephalopathy) [13].

In the most recent classification of the epilepsies [12, 13], the term “genetic” was included as a seizure etiology. This term includes patients with all genetic mutations including patients with a de novo mutation that occurs in a patient without a family history of epilepsy. An increasing number of de novo genes are being associated with mild to severe epilepsies [19, 20]. Genetics additionally play a role to determine some metabolic such as lysosomal storage disorders, amino- and organic acidopathies and mitochondrial disorders.

A very brief history of the heredity and genetics of epilepsy

Epilepsy is a phenotypically heterogeneous group due to many etiologies that involve complex interactions between environmental factors as well as the role of several or many genes. The concept of epilepsy as an inherited condition dates back to at least 400 BCE in *On the Sacred Disease* by Hippocrates [21]. It was estimated by Gowers that 30% of his case series had a heritable form of epilepsy [22]. In 1903, Lundborg [23] published on the genetics of progressive myoclonic epilepsy that was first described by Heinrich Unverricht (1868–1943) in 1891 and hypothesized a connection between heredity and epilepsy. He traced the disease in one extensive kindred back to the 1700s. Auguste Marie was asked by the ILAE to write a letter that led to the formation of the ILAE in which he mentioned that “epilepsy may be a problem of “hereditary, or result from a variety of acute and chronic infections” [24].

Between 1935 and 1937, Conrad demonstrated in his series of patients that the rate of epilepsy in monozygotic twins was 56% whereas dizygotic twins had an occurrence in 5% [9]. In 1933, there was a statute passed in Nazi Germany that “protected” descendants of people with a “hereditary disease.” This was the Law for Prevention of Genetically Diseased Offspring or the “Sterilization Law.” Due to their understanding of genetics, this law invoked sterilization of any citizen with a “genetic disorder,” including “hereditary epilepsy.”

Throughout the years, the types and understanding of the genetics have changed. The first of the recent studies on epilepsy genetics were based on Mendelian genetics that relied on large pedigrees [25]. The inheritance was autosomal dominant in many of the familial epilepsy syndromes where the mutations were identified and provided evidence that epilepsy was genetically influenced. Metrakos and Metrakos provided further evidence on the genetics of epilepsy by studying the centrencephalic type of EEG. They found the centrencephalic type of EEG was expressed as an autosomal dominant gene with a very low penetrance at birth [26]. This conclusion was based on analysis of probands with their parents and siblings. Thirty seven percent of siblings with probands with centrencephalic epilepsy had similar EEG patterns regardless of whether or not they had clinical seizures. Other studies reported similar findings with 15% of the siblings having seizures and rolandic discharges, and 19% having rolandic discharges alone [27].

The term genetic epilepsy is used when a seizure is the core symptom of a known or presumed genetic mutation. Gene abnormalities can occur due to several types of mutations. A germline mutation is inherited because it is a variation in the sperm or egg cell that is passed directly from a parent to a child at the time of conception. A somatic mutation is an alteration in DNA that occurs after conception and occurs in any of the cells except the germ cells and therefore are not passed on to children. Lastly, there are sporadic mutations that occur in a gene and are not present in either parent. When gene mutations are inherited, there can be variable penetrance and therefore their phenotype may be different in individual family members. Genetic epilepsies are associated with generalized and focal epilepsies as well as the epileptic encephalopathies. It is important to consider that the term “genetic” does not necessarily mean “inherited” [28]. This can exist because a patient can have an underlying causative genetic mutation known that is not inherited from either parent. The gene mutation in this case is de novo. Also, the genetic mutation can be inherited but not fully penetrant. In this case, the individuals carrying the mutation are unaffected.

One can determine a genetic etiology based on three inferences explained by Scheffer [13]. The first inference is based on a family history of autosomal dominant disorders. In some syndromes (e.g., self-limited neonatal epilepsy (SeLNE), many of the patients have different mutations in the same gene or in one of the potassium channel genes (*KCNQ2* or *KCNQ3*), whereas in others [sleep related hyperkinetic (hypermotor) epilepsy (SHE), previously autosomal dominant nocturnal frontal lobe epilepsy], there is a pathogenic gene variant in about 19% of autosomal dominant sleep-related hypermotor

epilepsy (ADSHE). However, there is a penetrance of approximately 70% [29]. In autosomal dominant nocturnal frontal lobe epilepsy (NFLE), there are genetic, genetic-structural, or acquired etiologies. Familial focal epilepsy with variable foci (FFFEVF), there is autosomal dominant inheritance with incomplete penetrance. Epilepsy with auditory features (EAF) may occur as a familial epilepsy syndrome (FEAF) with inheritance in an autosomal dominant fashion with reduced penetrance. Secondly, it is presumed that there is a genetic etiology by drawing conclusions from clinical research in twin populations regarding the genetic basis. Thirdly, a molecular basis has identified single genes or copy number variants that lead to major phenotypic differences. Due to different mutations within the same gene, the phenotype can present as mild to severe disease. Therefore, understanding the clinical spectrum associated with a specific mutation in a gene is critical since the gene mutation itself does not dictate clinical outcome. For instance, *SCN1A* can present with a broad clinical spectrum.

There is often a blurring between monogenic and polygenic background in the common epilepsies. Monogenic inheritance is an inheritance pattern determined by one set of alleles or a specific gene. Polygenic inheritance is an inheritance pattern which determines a particular trait by more than one set of alleles or more than one gene. Whereas some epilepsy syndromes have a clear single gene etiology with clear family history, the same epilepsy syndrome may appear sporadically without an identified gene. This implies that a complex genetic background must exist. Because there is variability in the expressivity and penetrance associated with monogenic epilepsies, other additional modifier genes and/or environmental factors influence the final phenotype of these genes. More than 20 genetic and structural epilepsies have been associated with single gene disorders. Single gene mutations can cause both generalized and focal epilepsies.

Current genetic testing

Clinicians are now testing more than before in patients with epilepsy and more genetic etiologies are being identified. The genetic testing that clinicians obtain include karyotype, chromosomal microarray, targeted gene panels, epilepsy gene panels, whole exome sequencing, and whole genome sequencing. There are different types of pathogenic genetic variants found in these panels. The genetic abnormalities can be due to a single base pair variation, insertion/deletions, (micro) deletion and (micro) duplication, aneuploidy, structural rearrangement, imprinting disorders, or mosaicism. With the increase in comprehensive genetic testing, genetic results of variants of unknown significance (VUS) are becoming more common. On occasion, the lab can re-classify the variant

to either pathogenic or benign so knowledge about these syndromes is always changing. Besides diagnosing the epilepsy syndrome, genetic testing can be used to determine whether certain antiseizure medications may be harmful to certain patients. For instance, patients with a polymerase subunit gamma (*POLG*) mutation cannot receive valproic acid [30].

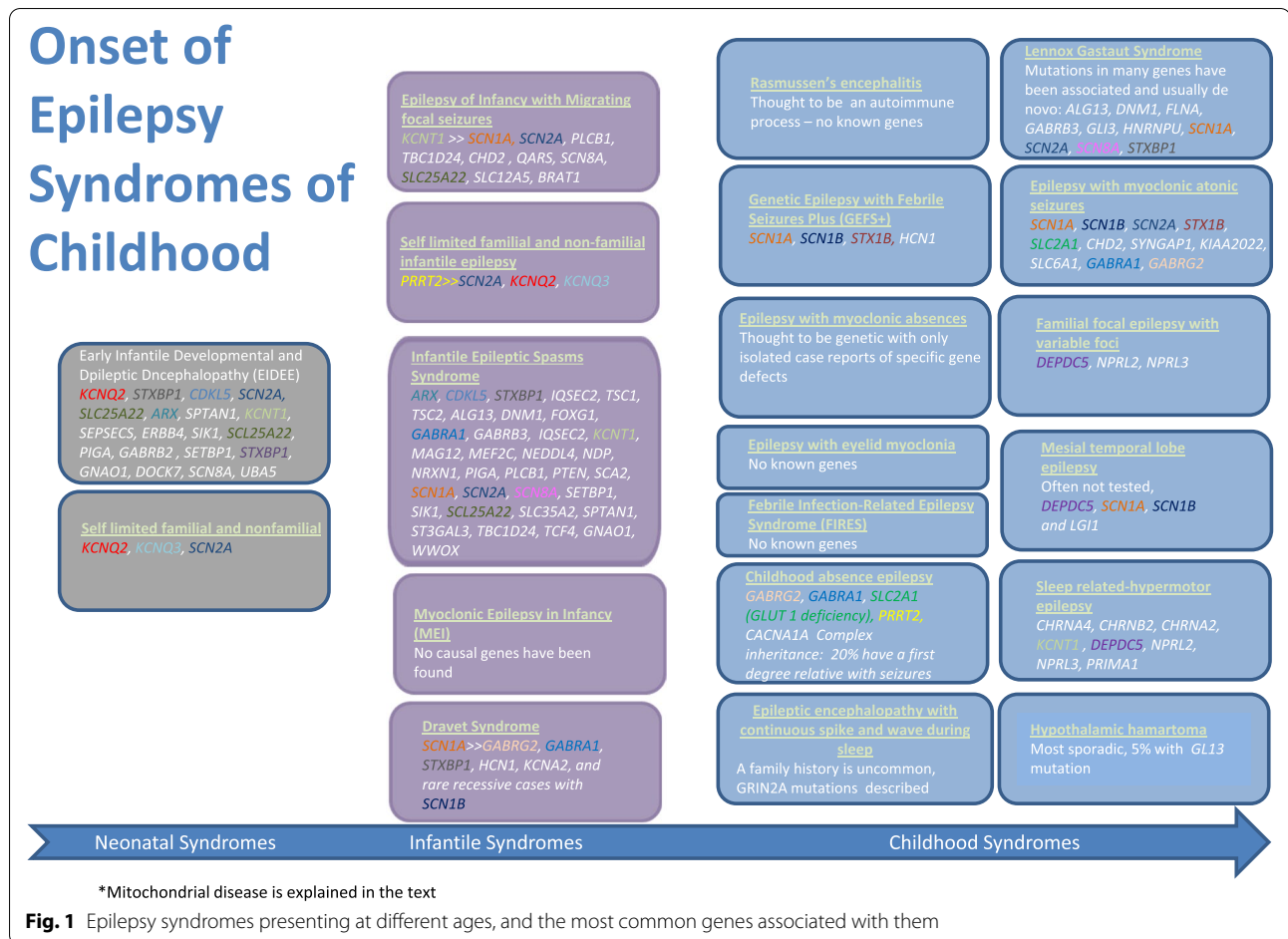
Specific gene panels as well as exome or genome sequencing can be helpful when some relative specific phenotypic features are considered to be consistent with already identified genes. Common genetic epilepsies can be tested initially with an array CGH and single nucleotide polymorphism (SNP)-microarrays, collectively referred to as chromosome microarrays (CMA) and can be used with a detection rate of 15%. Karyotype can also be obtained to detect abnormalities (e.g., ring chromosome 14.) Gene panels can now be widely obtained. Monogenic epilepsies and encephalopathies can be tested with a specific epilepsy panel or exome sequencing. Because fewer genes are sequenced in gene panels, their cost is less than whole exome sequencing or whole genome sequencing. This allows for more patients to undergo gene panels.

Genotype vs. phenotype

Specific gene mutations may be associated with different phenotypes. A genotype refers to the set of genes that an individual carries, whereas a phenotype is the clinical characteristics that are influenced by the individual's genes and environment. Specific genes have different variants that contribute to many diverse epilepsy phenotypes and syndromes.

Several genes are associated with both severe and self-limited pharmaco-responsive epilepsies, such as *SCN1A* or *KCNQ2*. As more genetic testing is being done, the range of phenotypes for each mutation in a gene is expanding and the clinical significance of certain defects is evolving. Additionally, a systematic literature review in neonatal seizures found that specific clinical seizure semiologies are more common in genetic etiologies of neonatal seizures and can guide further workup and clinically direct the workup to confirm the etiology [31].

A specific genotype can be seen in different epilepsy syndromes with drastically different phenotypes. Figure 1 illustrates childhood epilepsy syndromes that are grouped into the age of onset of the syndrome, although several syndromes occur in multiple age groups. In the syndromes presented, epilepsy is the main feature of the syndrome. However, there are other genetic syndromes that have epilepsy as part of the phenotype. Such examples include Rett, Angelman, Down, and Wolf-Hirschhorn syndromes as well as neuronal ceroid lipofuscinoses, holoprosencephaly, Wilson's disease,



tuberous sclerosis, and Niemann Pick disease, etc. With these different syndromes, it is important to acknowledge if the impairment is due to the underlying cause (DE) or due to the epileptiform activity (EE, DEE). One should acknowledge that not all syndromes have known genes or are genetic. For each syndrome with a known genetic mutation, only a percentage of the patients with the syndrome have an identified mutation. The percentage of identified genetic mutations fluctuate depending on the syndrome. In Dravet syndrome, which it is thought to be purely genetic, about 70–80% of patients carry *SCN1A* abnormalities. However, this is an exception. In other syndromes, the rates of gene abnormalities are much lower because of the low penetrance or no causal genes have been found.

Recent publications have evaluated the most common single genes found in children with epilepsy as well as their phenotypic expression. One study identified proline-rich transmembrane protein 2 (*PRRT2*) as the most common single-gene found in children with epilepsy less than 36 months of age [32] with 1 per 9970 live births, followed by *SCN1A*, *KCNQ2*, and *SLC2A1*. This study

found that a genetic diagnosis was typically found in patients who presented before the age of 6 months and demonstrated focal seizures. Another study looked at *HCN1* mutations and described its broad clinical spectrum of phenotypes [33]. This study evaluated patients with familial and sporadic gene abnormalities. The predominant phenotype was mild, presenting as a genetic generalized epilepsy or on the genetic epilepsy with febrile seizures plus (GEFS+) spectrum. About 20% were found to manifest a neonatal/infantile onset epileptic encephalopathy.

Below are examples of single gene disorders in structural epilepsies, idiopathic epilepsies, and focal epilepsy.

Tuberous sclerosis complex (TSC)

Tuberous sclerosis complex (TSC) is an autosomal dominant multisystemic disease with variable expression that is caused by a mutation in either the *TSC1* or *TSC2* gene. The gene defects are either mutational, sporadic, or familial. TSC is a leading genetic cause of epilepsy, and often presents with refractory seizures. Epilepsy affects 75–90% of people with TSC [34]. Seizure syndromes that

develop in people with this gene include infantile epileptic spasms syndrome (IESS), familial focal epilepsy with variable foci (FFEVF) [16], and Lennox-Gastaut syndrome (LGS).

DEP domain containing 5, GATOR1 subcomplex subunit (DEPDC5)

Mutations in *DEPDC5* encompass a range of epilepsy syndromes and has been identified in patients with familial focal epilepsy with a diverse phenotypical spectrum including SHE, FMTLE, FFEVF, infantile epileptic spasms syndrome, mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS), and EAF [16, 35]. It is inherited in an autosomal dominant manner, yet de novo mutations are also reported. Typically, the seizures are focal. It is usually associated with a normal MRI brain, however, in some cases, it can be associated with focal cortical dysplasia.

Potassium voltage-gated channel subfamily Q member 2 (KCNQ2)

Several phenotypes have been linked to mutant *KCNQ2* gene at chromosome 20q13. Mutations in this gene have been identified in families with self-limited (familial) neonatal epilepsy (SeLNE) and self-limited familial neonatal-infantile epilepsy (SeLFNIE) but also with an opposite phenotype in infants with neonatal *KCNQ2* epileptic encephalopathy [36] or *KCNQ2* developmental epileptic encephalopathy (*KCNQ2*-DEE) [18]. In the self-limited form, it can present with multiple seizure semiologies in otherwise healthy infants between the 2nd and 8th day of life and spontaneously disappear. It can also present with recurrent febrile seizures or developmental delays. Some affected children have recurrent febrile seizures, self-limited childhood epilepsy with central temporal spikes, or rare photosensitive myoclonic epilepsy [37]. In the more severe epileptic encephalopathy phenotype, it is characterized by multiple daily seizures beginning in the first week of life that are mostly sequential with a tonic component. The EEG is typically characterized by a burst-suppression pattern or a multifocal EEG. These children have intractable seizures and a grave neurologic prognosis.

Proline-rich transmembrane protein 2 (PRRT2)

Mutations in the *PRRT2* gene are a commonly occurring genetic mutation that can present with a spectrum of phenotypes [32]. The mutation most frequently presents as self-limited (familial) infantile epilepsy (SeLIE) [18]. However, it can be associated with other phenotypes including febrile seizures, childhood absence epilepsy, migraine, or hemiplegic migraine [38]. With next-generation sequencing, the clinical spectrum continues to

evolve and includes a spectrum of paroxysmal diseases [39].

Sodium voltage-gated channel alpha subunit 1 (SCN1A)

Several epileptic syndromes have been linked to sodium channel neuronal type 1A subunit mutations. While more than 80–90% of patients with Dravet syndrome have a pathogenic variant of *SCN1A*, mutations in this gene have a variable phenotypic expression. Dravet is therefore a clinical, and not a gene diagnosis. *SCN1A* is associated with Dravet syndrome as well as GEFS+ spectrum and epilepsy with myoclonic atonic seizures. Mutations in the sodium channel neuronal type 1A subunit account for the 10% of patients with GEFS+. These patients present with a milder clinical severity and usually normal development [40]. GEFS+ is more commonly multifactorial with complex genetics because of its heterogeneous phenotype [41]. It is worth noting that GEFS+ also can present with mutations in the *SCN1B* and *SCN2A* gene as well as the *GABRG2* gene and *STX1B* gene as identified below. *SCN1A* is also present in epilepsy of infancy with migrating focal seizures (EIMFS) [18], EAF, and MTLE-HS [16]. *SCN1A*-DEE is distinguished from Dravet syndrome by its onset that is less than 3 months [18].

Syntaxin 1B (STX1B)

STX1B is a gene that can cause fever-associated epilepsies with also variable phenotypic expression [42]. It presents with either a benign course of GEFS+ syndrome or with a more severe epileptic encephalopathy phenotype (*STXBPI*-DEE) [18] or epilepsy with myoclonic atonic seizures (EMAtS). The DEE variant is associated with asymmetric tonic or sequential seizures. A recent study looked at *STX1B*-related epilepsies identified 4 different phenotypes as well as 17 new variants [43]. The four different phenotypes identified included a: (1) a benign course of GEFS+, (2) a generalized epilepsy, (3) a developmental and epileptic encephalopathy, (4) focal epilepsy phenotype [43].

Genetics of developmental epileptic encephalopathies (DEE)

Developmental epileptic encephalopathies consist of a large heterogenic group of severe epilepsy. It occurs in infants and children with severe and intractable epilepsy as well as developmental impairment. They consist of many age-related electroclinical syndromes with specific seizure types and EEG features. There are more than 50 known genes that have been determined to cause epileptic encephalopathies, and the number is growing rapidly. The gene mutations may be inherited or can occur de novo. Additionally, several genes can cause the same electroclinical syndrome. Examples of such affected genes include, but are not limited to, *ARX*

, *GNAO1*, *SCN2A*, *SCN8A*, *STXBPI*, *KCNQ2*, *CDKL5*, *SLC25A22*, *SPTANI*, *KCNT1*, *UBA5*, and *SEPSECS*. It has been found that certain mutations may be associated more with certain seizure types. For example, *SCN2A* mutations are seen with sequential seizures with predominantly tonic and autonomic seizures [44], whereas *STXBPI* mutations are associated with asymmetric tonic or sequential seizures (tonic, autonomic, clonic, and epileptic spasms) [45, 46], and *KCNT1* can present with focal tonic seizures with autonomic symptoms [47].

Genetics of focal epilepsies

The genetics of focal epilepsy are also rapidly evolving. The etiology is genetic with higher incidence of epilepsy in families and a familial EEG traits [16]. Many familial focal epilepsy syndromes have been discovered [48–51]. The *CHRNA4* mutation was found in sleep related hypermotor epilepsy (SHE) (previously autosomal dominant nocturnal frontal lobe epilepsy) in 1995 [52]. *KCNQ2* and *KCNQ3* were discovered shortly after that time. Now there are many genes and chromosomes identified for SHE, including the *CHRNA4* gene that can be linked to chromosome 20q13.2 or 15q24 [53], as well as *CHRNA2*, *CHRN2*, *DEPDC5*, *KCNT1*, *NPRL2*, *NPRL3*, *PRIMA1*. The phenotype seems to be similar despite the diversity in the genes coding for the different *CHRN* subunits [54]. Additional genes that cause focal epilepsies include *TSC1*, *TSC2*, as well as genes encoding components of the GATOR1 complex including *DEPDC5*, *NPRL2*, and *NPRL3* [48]. This is a negative modulator of the mammalian target of rapamycin (mTOR) pathway. The “mTORopathies” are due to dysregulation of the mTOR pathway and are seen in various malformations of cortical development that are often associated with focal epilepsy.

Self-limited focal epilepsy syndromes (SeLFEs) such as Self-limited epilepsy with centro-temporal spikes (SeLECTS) may be associated with specific genes. The genetic basis of SeLECTS is largely unknown and, in most children, there are no identified pathogenic genes. Several studies have found possible associated genetic mutations. It has also been found that *GRIN2A* has been associated with focal epilepsy, ranging from SeLECTS to developmental and/or epileptic encephalopathy with spike-wave activation in sleep [55]. Other focal epilepsies including SHE, FMTLE, FFEVF, and EAF are associated with specific related genes [16].

Genetics of generalized epilepsies

Genetic generalized epilepsies including childhood absence epilepsy (CAE), epilepsy with myoclonic atonic seizures, and Lennox-Gastaut syndrome have a strong

genetic component. The majority of patients have multiple genes that can cause the same epilepsy syndrome. Only a few genes associated with CAE are known (e.g., *GABRG2*, *GABRA1*, *SLC2A1*). There are some recurrent copy number variants associated with CAE (e.g., 15p13.3). While most children do not have an identified gene mutation in epilepsy with myoclonic atonic seizures, mutations in various genes, including *SCN1A*, *SCN1B*, *SCN2A*, *SLC2A1*, *CHD2*, *SYNGAP1*, and *KIAA2022*, have been identified in some cases. Mutations in many genes have been associated with LGS and are usually de novo in the child. A range of chromosomal abnormalities and copy number variants have also been associated [56]. In the idiopathic generalized epilepsy (IGE) syndromes, there is a complex inheritance that may be due to a polygenic basis. In a small proportion of IGE patients, monogenic causes have been identified [17].

Mitochondrial diseases and epilepsy

Mitochondrial respiratory chain disorders are relatively common inborn errors of energy metabolism. Some of the mitochondrial diseases have seizure as part of the described phenotype. Seizure may be the presenting feature of mitochondrial disease but is often part of a multisystem clinical presentation. Seizures are seen in such diseases including mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) as well as myoclonic epilepsy with ragged red fibers (MERRF). Additionally, mutations in DNA *POLG* have been associated with seizures and has important implications in treatment options since it is thought that treatment with valproic acid can cause fulminant liver failure in these patients. *POLG* has classically been associated with Alpers syndrome but also can present as other mitochondrial syndromes with seizures. These syndromes often have seizures that are intractable and at present, there are no curative treatments.

Presumed treatments

The eruption of genetic techniques over the last couple of years have identified specific genetic mutations associated with epilepsy syndromes taking into account the caveats discussed above [57]. This led to possible discovery of more precise treatment options, with a gradual change in the therapeutic considerations. It is assumed (or more precisely hoped) that once a certain gene is determined it can have therapeutic relevance.

Voltage gated sodium channels are therapeutic targets of frequently used antiseizure medications including phenytoin, carbamazepine, and lamotrigine. Depending on the genetic mutation, these medications may either be helpful or harmful. For certain syndromes, such as Dravet syndrome with *SCN1A* mutation (a loss

of function mutation), it is thought that sodium channel agents should be avoided since there is some evidence that they may exacerbate seizures [58, 59]. Whereas, in other syndromes, such as *KCNQ2* encephalopathy or *SCN8A* mutations (gain of function mutation), sodium channel blocking agents have been shown to be effective in some cases in stopping the seizures [60]. In epilepsy with myoclonic atonic seizures, carbamazepine and vigabatrin may be associated with exacerbation of seizures and myoclonic status [59]. There are certain medications that may be precise for certain genetic mutations. For instance, *KCNT1* gain of function mutation has been shown to be reversed by treatment with quinidine [61, 62]. However, it is not effective in all children with the mutation [63]. Disorders associated with *Glut1* mutation are best treated with the ketogenic diet, and valproic acid should be avoided in patients with *POLG* mutations. Lastly, patients with *CACNA1A* mutation may exhibit some response to acetazolamide [64, 65].

Despite our current understanding of genetics and treatment, there is no one antiseizure medication that works every time in a specific syndrome. In most cases, when the appropriate medication is chosen, there is symptomatic relief; however, there may also be no benefit or even worsening despite appropriate treatment.

Ethical concerns with genetic testing

Historically, the notion of heritability of epilepsy has led to stigma and discrimination against people with epilepsy. In some instances, individuals with epilepsy have been institutionalized, underwent forced sterilization, and had prohibitions on marriage and immigration [21, 66]. With the advances in genetic testing, there are ethical, legal, and social considerations that require careful discussion with the patient and their family before the testing is obtained. Genetic testing must include autonomy, informed consent, confidentiality, and privacy of the genetic information. The results of the testing can influence health and life insurance coverage, employment, and can cause increased psychological stress. In some populations, there is significant stigma that has arisen with genetic testing. In such populations, it is thought that the familial lineage is tainted with a “genetic diagnosis” and that such a diagnosis can influence one’s ability to be married as well as the family’s social status. A patient can have a de novo mutation that has arisen sporadically without a family history of epilepsy. However, it can be possible to have a de novo dominant mutation that can be passed down to their children.

Conclusions

Genetics play a role in all areas of brain development and clinical expression. Gene identification can aid in diagnosis and is important in prevention and counseling families affected by a genetic condition. Depending on the gene involved, there are different responses to medication or surgical treatment that may be more appropriate and can alter treatment decisions. For example, tuberous sclerosis may involve cortical resection to achieve seizure freedom.

Epilepsy syndromes and their genetics have been rapidly changing as new gene technologies are being developed. Understanding genetics can help clarify the syndrome and its treatment. The syndromes have been revised, updated, and recycled as more information is gathered and the genetics are better understood. It is remarkable to see how far we have come in the understanding of the etiology of epilepsy including genetic testing, gene therapy, and its influence in treatment / management decisions. New knowledge on genetic etiologies of epilepsy syndromes is influencing pharmacological and surgical therapies. Epilepsy is a field of active research. Over the next few decades, the growing evidence of genes and epilepsy is on the cutting edge of modern epilepsy research and will lead to new discoveries that will change the field of epilepsy to improve patients quality of life by creating new means of preventing, controlling, and curing epilepsy.

Abbreviations

ADSH: Autosomal dominant sleep-related hypermotor epilepsy; CAE: Childhood absence epilepsy; CMA: Chromosomal microarray; DE: Developmental encephalopathy; DEE: Developmental and/or epileptic encephalopathy; DEPDC5: DEP domain containing 5, GATOR1 subcomplex subunit; DNA: Deoxyribonucleic acid; EAF: Epilepsy with auditory features; EE: Epileptic encephalopathy; EEG: Electroencephalogram; EIDEE: Early infantile developmental and epileptic encephalopathy; EIMFS: Epilepsy of infancy with migrating focal seizures; EMAtS: Epilepsy with myoclonic atonic seizures; FFEVF: Familial focal epilepsy with variable foci; GEFS+: Genetic epilepsy with febrile seizures plus; IESS: Infantile epileptic spasms syndrome; IGE: Idiopathic generalized epilepsy; ILAE: International League Against Epilepsy; KCNQ-DEE: *KCNQ2* developmental epileptic encephalopathy; LGS: Lennox-Gastaut syndrome; MELAS: Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; MERRF: Myoclonic epilepsy with ragged red fibers; MRI: Magnetic resonance imaging; MTLE-HS: Mesial temporal lobe epilepsy with hippocampal sclerosis; NFL: Nocturnal frontal lobe epilepsy; POLG: Polymerase subunit gamma; PRRT2: Proline-rich transmembrane protein 2; SeLECTS: Self-limited epilepsy with centrotemporal spikes; SeLFe: Self-limited focal epilepsy syndrome; SeLFNIE: Self-limited familial neonatal-infantile epilepsy; SeLIE: Self-limited (familial) infantile epilepsy; SeLNE: Self-limited neonatal epilepsy; SHE: Sleep related hyperkinetic (hypermotor) epilepsy; SNP: Single nucleotide polymorphism; STX1B: Syntaxin 1B; STXBP1-DEE: Syntaxin 1B epileptic encephalopathy phenotype; TSC: Tuberous sclerosis complex.

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