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PEDIATRIC NEUROLOGY (P PEARL, SECTION EDITOR)

The Genetics of the Epilepsies

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Abstract While genetic causes of epilepsy have been hypothesized from the time of Hippocrates, the advent of new genetic technologies has played a tremendous role in elucidating a growing number of specific genetic causes for the epilepsies. This progress has contributed vastly to our recognition of the epilepsies as a diverse group of disorders, the genetic mechanisms of which are heterogeneous. Genotype-phenotype correlation, however, is not always clear. Nonetheless, the developments in genetic diagnosis raise the promise of a future of personalized medicine. Multiple genetic tests are now available, but there is no one test for all possible genetic mutations, and the balance between cost and benefit must be weighed. A genetic diagnosis, however, can provide valuable information regarding comorbidities, prognosis, and even treatment, as well as allow for genetic counseling. In this review, we will discuss the genetic mechanisms of the epilepsies as well as the specifics of particular genetic epilepsy syndromes. We will include an overview of the available genetic testing methods, the application of clinical knowledge into the selection of genetic testing, genotype-phenotype correlations of epileptic disorders, and therapeutic advances as well as a discussion of the importance of genetic counseling.

Keywords Epilepsy · Epileptic encephalopathy · Epilepsy syndrome · Channelopathies · Genetics · Channelopathies

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Introduction

The understanding of epilepsy has been rapidly growing with the expansion of genetic discoveries and new genetic technologies [1]. In 1975, the majority of the epilepsy was classified as idiopathic, with a minority attributed to trauma, cerebrovascular accidents, tumors, infections, and other causes [2].

Now in 2015, the term "idiopathic" is being phased out of the classification lexicon in lieu of genetic. The genetic mechanisms and factors behind multiple epilepsy syndromes have been elucidated, and more so recently with the advent of whole exome sequencing [3].

The earliest recognition of the inheritance of epilepsy was related to single-gene familial epilepsies as well as established syndromes frequently featuring epilepsy. Still, it is recognized that some patients with genetically based epilepsy are not explained by monogenic inheritance but instead a complex combination of genetic and possibly non-genetic factors.

While the clinical applications are in their very early phases, the influx of genetic information is allowing for more accurate diagnosis, counseling, and in certain cases, therapy.

Genetic Mechanisms of the Epilepsies

The genetic causes of epilepsy encompass multiple mechanisms:

Chromosomal copy number abnormalities include monosomies and trisomies of whole chromosomes as well as microdeletion/duplications that involve smaller chromosomal regions.

Genomic rearrangements are structural genomic changes with size ranging from a few hundred base pairs to megabases (Mb). These include duplications, deletions, insertions, inversions, translocations, and ring chromosomes. Copy number variations (CNVs) are a type of genomic rearrangement defined as 1-kb DNA segments or larger presenting in a different copy number when

compared to the reference genome. CNVs mainly consist of microdeletions and microduplications, occasionally with more than one additional copy.

Trinucleotide repeats can cause neurological disorders when a trinucleotide unit near or within a gene reaches an expansion threshold.

Single-nucleotide alterations can result in missense, frameshift, or non-sense mutations.

Genomic imprinting constitutes yet another mechanism that contributes to the genetics of the epilepsies, whereby gene expression is dependent on the parent of origin of a particular allele. The best examples of these disorders are Prader-Willi Syndrome (PSW) and Angelman Syndrome (AS). PWS and AS are two distinct disorders, which both result, in most cases, from a 15q11-13 deletion. Deficiency, in most cases, of the paternally expressed *SNORD116* gene through paternal inheritance of the deletion, maternal uniparental disomy, or imprinting defect results in PWS, while loss of function of the UBE3A gene through maternal inheritance of the deletion, imprinting defect, paternal uniparental disomy, or UBE3A gene mutation results in AS [4].

Imprinting center (IC) mutations are inherited microdeletions, best described in a "single genetic element" of the 15q11-13 chromosome region. The IC regulates DNA methylation and gene expression throughout the entire 15q11-13 region, and microdeletions of the IC lead to aberrant DNA methylation of the imprinted region. These mutations are found in a subset of patients with Prader-Willi Syndrome (PSW, 1–3 %) and Angelman Syndrome (AS, 2–4 %) [4, 5].

Genetic abnormalities can be inherited from one or both parents, or can arise de novo either in a parental gamete (germline mutations) or after fertilization (somatic mutations). Somatic mutations are regular occurrences during development leading to different populations of cells. When involving CNS progenitor cells, they can result in disruption of neuronal networks and potentially epileptogenesis [6, 7]. An example of somatic mutations causing epilepsy is Sturge-Weber syndrome with *GNAQ* mutations found in the affected tissue [8]. Certain somatic mutations have been shown to affect the brain only, for example, *AKT3* and *PI3K* mutations in isolated hemimegalencephaly [9–11, 12•].

There are also examples of dominant inheritance from mildly affected, or even unaffected, parents. Known mechanisms include somatic mutations in the parent, incomplete penetrance, epigenetic factors, and effects from modifier genes [13, 14]. Data from mouse models suggested a role of *SCN8A* in modifying the phenotype of *SCN1A*-associated epilepsy [15], while clinical data identified *SCN9A* gene mutations as independently pathogenic or phenotypic modifiers in *SCN1A* mutation associated epilepsy [16].

Multiple mechanisms of pathogenesis have been identified using functional analysis, mainly in monogenic epilepsies. A well-identified mechanism is that of channelopathies, mainly affecting sodium and potassium channels. The most commonly mutated gene in epilepsy is *SCN1A*, encoding a sodium channel, and resulting in severe myoclonic epilepsy but also a milder phenotype known as genetic epilepsy with febrile seizures plus, or GEFS+. Mutations in *SCN1B*, *SCN2A*, *SCN3A*, *SCN8A*, and *SCN9A* have been also found to contribute to seizure disorders [17]. Mutations in potassium channel genes *KCNQ2* and *KCNQ3* also result in a variety of epilepsy phenotypes [18, 19]. Other mechanisms include DNA transcription regulation (e.g., *ARX*) [20], cell-cell adhesion and synaptic connection (e.g., *PCDH19*) [21], modulation of synaptic vesicle docking and release (e.g., *STXBP1* and *SPTAN1*) [22], synaptic vesicle endocytosis (e.g., *DNM1*) [23], cell signaling (e.g., *CDKL5* and *PLCB1*) [24, 25], DNA repair (e.g., *PNKP*) [26], and enzyme function in metabolic pathways (e.g., *PNPO*) [27, 28].

Tools for Genetic Testing in Epilepsy

There are multiple techniques that can be used for genetic evaluation in epilepsy patients. It is important to note that there is no single technology screen for all genetic mechanisms [29].

Chromosomal microarray analysis (CMA) evaluates for copy number variations (deletions and duplications). This technique uses either single-nucleotide polymorphism (SNP) array or array-comparative genomic hybridization with oligonucleotide probes. It is especially indicated when epilepsy co-occurs with developmental delay, autism spectrum disorder, or dysmorphic features. One of the main advantages is the inclusion of both targeted and untargeted loci, which provides a survey of all chromosomes. CMA is relatively fast, and results are available within a few weeks.

Karyotypes are photographic representations of all the chromosomes in one cell, arranged in pairs based on size and banding patterns. While karyotype in the past was performed initially in patients with dysmorphic features, multiple congenital anomalies, suspected trisomies, or monosomies, CMA is now the preferred modality since it offers much greater resolution. However, karyotype may still be useful in the epilepsy setting if there is a suspected complex chromosomal rearrangement (e.g., ring chromosome).

Single-gene sequencing evaluates for sequence alterations, and whether the alterations result in a single amino acid change, frameshift, or stop-gain. This approach is most helpful when a specific genetic abnormality is suspected.

Single-gene duplication and deletion analysis evaluates for CNVs in targeted genes, at the exon level, and is useful when single-gene sequencing is negative and an abnormality in that

gene is still suspected. In this case, it is more sensitive than chromosomal microarray.

Targeted mutation analysis is another sequencing method, which looks only for a specific mutation(s). This approach should be used for parental testing to determine whether a variant in a patient is inherited, which may influence the interpretation of whether it is pathogenic or of unknown significance, depending on the gene in many cases. Targeted analysis is also used in common mutations associated with specific and clinically distinct disorders such as m.3243A>G point mutation in a mitochondrial tRNA gene, the most common cause of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) [30]. In addition, for recessive diseases, targeted testing evaluates for carrier status. It is faster and less expensive than gene panel testing.

Targeted gene panels include sequencing, with or without duplication and deletion testing, specific to a syndrome, disorder, or group of disorders, for example, early-onset epileptic encephalopathy or febrile seizure panels. The technology most commonly used is next-generation sequencing (NGS) which has largely replaced Sanger sequencing. As opposed to Sanger sequencing method which was only capable of handling a limited number of samples in parallel, NGS allows for massively parallel sequencing in a much shorter period of time (weeks as opposed to years). However, once a mutation is recognized through NGS, validation by Sanger sequencing can add more accuracy to the result.

In some situations, sequencing and deletion/duplication testing is not sufficient to comprehensively assess whether a gene or genes are involved. For example, methylation studies in a specific chromosomal region (chromosome 15q) are used if a disorder such as Prader-Willi or Angelman syndrome is suspected.

Fluorescent in situ hybridization (FISH) is a technique that uses fluorescently labeled probes that identify the presence or absence of specific chromosomal regions and is best used to confirm deletion or duplication in a specific region.

Whole-exome sequencing (WES) evaluates for sequence changes throughout the coding sequence of all ~30,000 genes in the genome. When other genetic testing is unrevealing and a genetic diagnosis is strongly suspected, WES should be performed. While WES is proving to be a very helpful tool [31], particularly when a "trio" approach is used (sequence patients and parents to more easily assess which potentially pathogenic variants are de novo), it has some limitations including the inability to identify CNVs, methylation abnormalities, or abnormalities in non-coding regions. It is an expensive method, but the costs are expected to decline over time. Given the large amount of data generated from a single exome, incidental findings are not uncommon. As with all genetic testing, genetic counseling is important before and after WES.

Whole-genome sequencing (WGS) evaluates for sequence changes throughout the entire genome, expanding on the coverage provided by WES to involve the non-coding regions. Its use in clinical practice is just beginning.

Somatic mosaic mutations are ideally tested by targeted or untargeted sequencing of affected and unaffected tissue. While brain tissue is rarely readily available, options can include a small proportion of easily accessible cells, such as fibroblasts and leukocytes. For this reason, single-cell and ultra-deep sequencing are needed to identify and measure the extent of somatic mutations in different cell types [9]. Some of these tests are commercially available, but they remain largely confined to research laboratories.

Functional analysis is not a readily available clinical tool. It is typically used to research or confirm the functional outcome of a new genetic mutation. The use of animal models (e.g., rodents and zebrafish), as well as patient-derived induced pluripotent cells (iPSCs), has been increasingly used to improve our understanding of the pathogenic mechanisms of mutations [32, 33, 34•].

Genetics of Epilepsy Syndromes

As described previously, many genetic mechanisms have been identified to be responsible for multiple epilepsy syndromes. It is important to note that different mechanisms can lead to similar phenotypes or similar groups of disorders, and similar mechanisms can result in different clinical syndromes.

Channelopathies are such an example. For example, *SCN1A* mutations are associated with Dravet syndrome but also with milder phenotypes such as genetic epilepsy with febrile seizures plus (GEFS+) [35]. *KCNQ3* mutations are associated with benign neonatal seizures while *KCNQ2* can be associated with early-onset epileptic encephalopathy or benign neonatal seizures, highlighting phenotypic variations resulting from mutations in the same gene [18, 36].

According to the International League Against Epilepsy, epilepsy syndromes are classified based on the electroclinical features and age of epilepsy onset [37]. It is therefore clinically relevant to understand the diverse genetic mechanisms of each of these syndromes as they might shed a light on diagnosis, treatment, and prognosis:

(a) Early-onset epileptic encephalopathies (EOEEs)

EOEEs are a group of disorders characterized by epilepsy, developmental impairment, and interictal epileptiform discharges starting in the neonatal period or early infancy. These include Ohtahara syndrome (OS), early myoclonic encephalopathy (EME), Dravet syndrome, infantile spasms, and epilepsy of infancy with migrating focal seizures (EIMFS), which was previously called migrating partial seizures of infancy (MPSI) [38]. A genetic etiology for EOEE was identified in around 20 % of cases via trio exome sequencing followed by Sanger

sequencing confirmation [39•]. More recent data have shown that a genetic etiology can be identified in more than 50 % of patients with OS without brain malformation, with the most frequently encountered mutation being KCNQ2 in 29 % of patients. These mutations were identified via NGS and/or WES [40].

Generally, the first step in diagnosis is to evaluate for a cerebral structural abnormality and metabolic errors and then consider genetic testing. If the patient's presentation fits a particular phenotype for a single gene, it is both cost-effective and time saving to begin with testing that particular gene. A gene panel, however, might be more helpful if the presentation could be consistent with a mutation, or deletion, in one of several genes. CMA should also be considered as it might identify potentially pathogenic copy number variations in regions containing epilepsy genes or within epilepsy genes. Ultimately, if the etiology remains unknown, WES may be needed, especially as more genes are discovered and are not immediately incorporated into panels.

OS is characterized by early-onset tonic spasms with burst suppression pattern consistently present in wakefulness and sleep [41]. It is most commonly associated with underlying structural brain malformations but is related, in other cases, to mutations in a variety of genes (e.g., *STXBP1*, *KCNQ2*, *SCN2A*, *ARX*, *SLC25A22*, *CDKL5*, *PNPO*, *BRAT1*, *CASK*, and *PIGA*) [19, 22, 42–48].

EME is distinguished from OS by the predominance of myoclonic seizures with burst suppression pattern more prominently seen in sleep. The etiology is typically metabolic and/or genetic, which overlaps with the genes listed above for OS. EME and OS often overlap clinically and with regards to etiology.

Dravet syndrome, or severe myoclonic epilepsy in infancy, is perhaps one of the most studied genetic epilepsy syndromes. It is associated with an identified mutation in the *SCN1A* gene in 70–80 % of the cases [49]. However, other genes have been found that cause Dravet, or Dravet-like clinical syndrome, including *PCDH19*, *SCN1B*, *STXBP1*, *GABRA1*, *CHD2*, *HCN1*, and *GABRG2* [21, 50–54].

EIMFS is an even more heterogeneous syndrome. While *KCNT1* mutations account for about one third of reported cases of EIMFS, the other genetically defined cases are caused by mutations in a number of other genes (*SCN1A*, *SLC25A22*, *PLCB1*, *TBC1D24*, *SCN2A*, *QARS*, *SCN8A*) [25, 55–61].

Infantile spasms (ISs) are a common manifestation of multiple genetic disorders [38, 62]. Given that infantile spasms are a symptom of a maturation-dependent severe brain dysfunction that can result from different pathophysiological mechanisms, the genetic etiologies of IS overlap with a multitude of other epilepsy syndromes. IS can develop after EOEE, or start anew and, in both cases, can transition into other epilepsy syndromes including Lennox-Gastaut syndrome (LGS).

Certain pathogenic CNVs have been found to be implicated in epileptic encephalopathies including EOEE, IS, and LGS, with "hot spots" including 16p11.2, 22q11, and 15q13.3 among others. These explain a small percentage of the epileptic encephalopathies [63]. De novo mutations in multiple genes have been described by the Epi4K consortium, with the phenotype including IS, LGS, or both. Mutations in *SCN1A*, *SCN2A*, *STXB1*, *SCN8A*, and *CDKL5* were found and had already been described in the literature as causative of epileptic encephalopathy. Genes known to be implicated in other neurological disorders were also found in epileptic encephalopathies and these include *MTOR*, *DCX*, and *FLNA*. These genes are classically associated with brain malformations. The newly identified genes included *GABRB3* and *ALG13* [23, 64]. In combination with the Epi4K consortium, the EuroEpinomics consortium confirmed de novo mutations in *DNM1* to be pathogenic [23].

Some of the known genetic mechanisms of IS are outlined in Table 1.

(b) Benign familial neonatal/infantile seizures

Genetic causes include channelopathy causing mutations (e.g., *KCNQ2*, *KCNQ3*, and *SCN2A*), as well as *PRRT2* present in the 16p11.2 chromosome region which is also associated with choreoatheosis syndrome [85]. Of note, *KCNQ2* and *SCN2A* have been associated with a more severe epilepsy phenotype such as early-onset epileptic encephalopathy, including Ohtahara Syndrome and EIMFS, as discussed above.

(c) Progressive myoclonus epilepsies (PMEs)

This group of epilepsies is characterized by myoclonic seizures and progressive neurodegeneration, typically starting in childhood or adolescence [86]. These disorders are rare, but multiple genes have been identified for the different subtypes.

The most common subtype, Unverricht-Lundborg disease (ULD), can be caused by mutations in *CSTB*, *SCARB2*, *PRICKLE1*, and *GOSR2* [87–89].

Lafora disease can be caused by *EPM2A* on 6q24.3 encoding laforin or *EPM2B* on 6p22.3 encoding malin, with data suggesting that the latter mutation causes a milder phenotype [90–92].

Neuronal ceroid lipofuscinosis (NCL) can be caused by a multitude of mutations, usually dictating the subtype of NCL: *CLN1* in classic infantile-onset form, *CLN2*, *CLN5*, *CLN6*, *CLN7*, and *CLN8* in late infantile-onset forms, *CLN3* in classic juvenile-onset form, *CLN4* and *CLN6* in adult-onset forms, and *CLN10* in congenital NCL which is the earliest in onset, and life expectancy

Table 1 Genetic mechanisms of infantile spasms

Mechanism	Specific genetic abnormality/syndrome	
Identified single genes	Associated with brain malformation	
	TSC1, *TSC2*: tuberous sclerosis complex	-IS in 38 %. Multiple seizure types, can develop into LGS [65]
	DCX	-Lissencephaly-pachygyria in males, subcortical band heterotopia in females [66]
	TUBA1A	-Lissencephaly, microcephaly [67]
	PAFAH1B1 (LIS1)/Miller Dieker Syndrome	-Lissencephaly, isolated subcortical laminar heterotopia, subcortical band heterotopia, choreiform movements [68]
	Channelopathies	
	SCN2A	-Wide spectrum; EOEE with transition to IS, GEFS+, BFN/IE, EIMFS [69]
	KCNQ2	-Wide spectrum, EOEE, mostly OS, with transition to IS, BFN/IE [70]
	Other mechanisms:	
	CDKL5: early seizure variant Rett syndrome in some	-Also seen in EOEE [71]
	FOXG1: atypical Rett syndrome/congenital Rett variant/ classic Rett syndrome	-Seen mainly in OS with transition to IS [22]
		-Tremors, acquired microcephaly, thin corpus callosum [72]
		-Frontal pachygyria, dyskinesias [73]
		-Also seen in Dravet syndrome [51]
	SLC525A22	-EOEE with transition to IS, also seen in EIMFS [45, 57]
	ARX	-Epileptic encephalopathy begins as IS or as EOEE with transition to IS [20],
		-Acquired microcephaly, lissencephaly, agenesis of corpus callosum [20, 74, 75]
		-Status dystonicus and dyskinetic cerebral palsy also reported [76]
		-Abnormal genitalia in boys [75]
	SPTAN1	-Epilepsy only reported with deletions, not point mutations
		-Milder EOEE phenotype with transition to IS, hypomyelination, acquired microcephaly [77]
	PLCB1	-Neurodegeneration, hypotonia, also EIMFS [25, 78]
	NF1 (neurofibromatosis type 1)	-Higher IS incidence than general population, classic IS, psychomotor delay precedes spasms [79]
	DNM1	-Hypotonia, +/− ataxia, +/−acquired microcephaly, no known structural abnormalities [23]
Chromosomal imbalance	1p36 deletion	-IS in 20 %, possibly associated with a potassium channelopathy (*KCNAB2*), brain structural abnormality is common, especially polymicrogyria [80, 81]
	Trisomy 21	-Classic IS in 1–13 %, favorable treatment response [82]
	Tetrasomy 12p (Pallister-Killian syndrome)	-IS and epileptic spasm at older age [83]
	15q11q13 duplication	-IS in 42 %, typically progress to LGS [84]

IS infantile spasms, *LGS* Lennox-Gastaut syndrome, *BFN/IE* benign familial neonatal/infantile seizures, *EOEE* early-onset epileptic encephalopathy, *OS* Ohtahara syndrome

is no more than days [93–95]. A recently identified PME mutation in *KCNC1*, encoding a subunit of a voltage-gated potassium channel, was found in 11 individuals with phenotype resembling classic ULD [96].

In addition to the above, the differential diagnosis of PME includes mitochondrial disorders such as myoclonic epilepsy associated with ragged-red fibers (MERRF) and sialidosis, with workup requiring different modalities including muscle biopsy or mitochondrial gene sequencing, and metabolic markers, respectively.

(d) Genetic generalized epilepsies

This term now preferentially replaces idiopathic generalized epilepsies, to describe disorders of presumed genetic etiology with epilepsy being the main feature. An important clinical example is *SLC2A1* mutations causing glucose transporter 1 deficiency, as it can present

with early-onset absence epilepsy or other generalized epilepsies such as typical childhood absence or juvenile myoclonic epilepsy, and should be considered in familial cases, difficult-to-treat seizures, paroxysmal dyskinesias, learning, or intellectual disability. The treatment of choice is ketogenic diet [97].

Copy number variations (CNV) of recurrent genomic hot spots have been frequently found in both genetic generalized and idiopathic focal epilepsies. These include 1q21.1, 15q11.2, 15q13.3, 15q11-q13, 16p11.2, 16p13.11, and 1q21.1 [98–102]. Interestingly, CNVs are more frequent in genetic generalized epilepsies with intellectual disability than in either of the phenotypes occurring independently [103].

Other identified genes are likely susceptibility genes for generalized epilepsies and include *CACNA1H*, *CACNB4*, and *CLCN2*, in addition to *CACNA1A*, which is associated with both focal and generalized seizures [104–107].

(e) Genetic epilepsy with febrile seizures plus (GEFS+) is associated with mutations in *SCN1A*, *SCN1B*, *SCN2A*, *GABRG2*, and *PCDH19* [21, 35, 69, 108].

(f) Familial focal epilepsies

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) can be caused by mutations in *CHRNA4*, *CHRNB2*, and *CHRNA2* genes [109]. The yield of genetic testing is around 20 and 5 %, with and without family history, respectively. These tests are considered to have a high clinical utility as the knowledge might affect clinical management, especially if surgery is a consideration [110]. Another important clinical aspect of testing in this situation is exemplified by the newly identified *KCNT1* mutations associated with severe ADNFLE [111]. Mutations in *KCNT1* can also be found in EIMFS, therefore justifying genetic testing when ADNFLE is a concern to allow for appropriate genetic counseling.

Other associations include *LGI1* mutations found in autosomal dominant partial epilepsy with auditory features or autosomal dominant lateral temporal lobe epilepsy [112, 113]. In the presence of positive family history, this test can be highly accurate and have a yield of around 50 % [114]. The clinical utility, however, is not as high as with ADNFLE, as most cases tend to have a benign course, and knowledge of the mutation does not typically alter clinical management [110].

A recently identified genetic mutation in familial focal epilepsy of different foci involves the *DEPDC5* gene, an mTOR pathway regulator. This mutation can be found in both lesional and non-lesional epilepsies, even within the same family [115]. The cortical malformations are hypothesized to result from a second genetic hit. *DEPDC5* mutations are also less frequently found in ADNFLE, familial temporal lobe epilepsy, rolandic epilepsy, and even hemimegalencephaly [116•, 117–120].

(g) Epileptic aphasias

The clinical spectrum of epileptic aphasias includes Landau-Kleffner syndrome (LKS), epileptic encephalopathy with continuous spike and wave during slow wave sleep (CSWS), and atypical rolandic epilepsy with speech impairment. Mutations in the *GRIN2A* gene, coding for the NR2A subunit of the NMDA receptor, have been found in these patients [121–124].

(h) Epilepsy with malformations of cortical development (MCD).

More than 100 genes have been found to be associated with MCD. Some of the neuronal migration and overgrowth disorders have been discussed so far throughout this review. These are a common cause of childhood epilepsy, and multiple genetic causes have already been identified. It is important to note that distinguishing epilepsy with cortical malformation from other genetic epilepsies is difficult and at times inaccurate, as there is overlap between genes associated with epilepsy with or without cortical malformations (e.g., 1p36 deletion, *FOXG1* mutations, and *SCN1A* mutations) [73, 81, 125].

Recently, somatic mosaic mutations have been increasingly recognized, in particular in association with overgrowth syndromes. Mutations in the PI3K-AKT-mTOR pathway were recently shown to cause a spectrum of brain overgrowth syndromes typically associated with epilepsy. Hemimegalencephaly (HME), with only one hemisphere being affected due to somatic mosaicism, as well as the more common focal cortical dysplasia (FCD), was seen in mutations of this pathway involving *PIK3CA*, AKT1, *AKT3*, or *MTOR* genes. Another example is megalencephaly (MEG) with capillary malformation (MCAP) syndrome which is mainly related to gain-of-function mutation in *PIK3CA* mutation. The typical findings include MEG and polymicrogyria. These mutations are typically not found in the blood and are only present in the affected cortex [9, 10, 114, 120]. In addition to somatic mutations, de novo germline mutations in this same pathway, involving *PIK3R2*, *CCND2*, and *AKT3* genes, have been found with megalencephaly-polymycrogyria-polydactyl-hydrocephalus (MPPH) syndrome [11].

Sudden Unexplained Death in Epilepsy and Genetics

the mechanism of sudden unexplained death in epilepsy (SUDEP) has yet to become fully elucidated. Certain genes are believed to be related to an increased risk of SUDEP. *SCN1A* is such a candidate as multiple cases of SUDEP have been reported in patients with GEFS+ or Dravet syndrome. The proposed mechanism is the expression of mutant *SCN1A*

channels in both the brain and the heart, possibly leading to fatal arrhythmias [126–130].

SCN8A mutation has been reported in a child with epileptic encephalopathy and SUDEP. The same mutation was studied in a rodent model and mice experienced seizures and SUDEP, with homozygous mice having a more rapid deterioration and earlier death [131, 132]. In a more recent study, 17 patients with epileptic encephalopathy and *SCN8A* mutation were clinically evaluated. Two of these patients died in early childhood, one during a seizure and the other from SUDEP [133]. *PHOX2B* was yet another candidate gene as it was found to be associated with sudden infant death syndrome in a Dutch cohort [134]. More recently, however, sequencing for *PHOX2B* gene in 68 patients who died of SUDEP did not reveal polyalanine expansion alleles or point mutations, therefore suggesting a lack of association between *PHOX2B* mutations and SUDEP [135•].

Epilepsy in Defined Genetic Syndromes

Numerous genetic syndromes feature epilepsy among multiple other clinical findings. The presence of epilepsy is at times the first clue to the diagnosis, and it is important to recognize these syndromes as the diagnosis might impact the management of other medical conditions. Relevant clinical examples include tuberous sclerosis complex, Angelman and Angelman-like syndromes, classical Rett and Rett variant syndromes, ring chromosome 14, ring chromosome 20, 15q tetrasomy, and 1p36 mutations.

The seizure characteristics of these disorders are summarized in Table 2.

Circumstances of Genetic Testing

The decision to perform genetic testing in epilepsy should always take into account the cost benefit ratio, as even if genetic testing is not considered invasive, it is not without risk and cost. The most valuable benefit is the direct impact the genetic information might have on treatment decisions. Even in the absence of targeted therapy, however, the information can provide other important benefits. For instance, data can be extrapolated from other patients with similar mutations to better understand the phenotype, as well as any associated morbidities and prognosis [110, 155]. This information is helpful for the patients, their families, and their health care provider. It is at times crucial for counseling, especially for families interested in having additional children. And, last but not least, the value of knowledge for the patients and their families should not be underestimated as, in many cases, genetic testing can give a definite and long sought after answer and can alleviate feelings of guilt or concerns about having caused the disorder whether directly or indirectly.

Clearly, in circumstances where the genetic testing would not affect clinical management, a balance must be struck between clinical suspicion and benefit to the patients and families.

Not unlike other genetically determined disorders, the value of genetic testing depends on the following four factors: analytic validity, clinical validity, clinical utility, and personal utility [29].

Features that suggest a genetic cause of epilepsy or an association with a genetic disorder include dysmorphic features or congenital abnormalities. In these situations, if a specific clinical genetic syndrome is not identified, it is best to start with broad genetic screening including a karyotype and a chromosomal microarray. The presence of autism spectrum disorder or autistic features and/or intellectual disability might also point to a genetic cause of epilepsy. Additionally, family history of epilepsy is a common reason to consider genetic testing.

Epilepsy due to brain abnormalities such as migrational defects or overgrowth syndromes is also typically associated with a genetic diagnosis. Targeted genetic sequencing or genetic panels are a good starting point. Whole-exome sequencing and in some cases deep sequencing which entails more intense and repeated sequencing of candidate genes (especially in the event of somatic mutations or mosaicism) can potentially add information if initial testing is negative.

Genetic Counseling in Epilepsy

Genetic counseling is key not only after a diagnosis has been made but also during the genetic testing decision-making process. Multiple questions continue to arise with the development of more and more genetic tests, including how to guarantee that individuals make informed decisions regarding testing, how to best interpret results to patients and families, and importantly, the impact, whether positive or negative, of these results. Incidental findings are not uncommon and might have a negative impact on patients and their families which underlines the importance of counseling [29].

The involvement of genetic counselors and physicians specialized in the field of epilepsy genetics has therefore gained tremendous importance. A multidisciplinary team approach is key to the success of programs in epilepsy genetics and neurogenetics to optimize counseling, diagnosis, and management.

Current Treatment in Genetic Epilepsies

Reversible or treatable genetic causes of epilepsy typically include those involving inborn errors of metabolism.

Table 2 Defined genetic syndromes: epilepsy and other clinical characteristics

Syndrome	Gene defect	Epilepsy characteristics	Other clinical features
Tuberous Sclerosis Complex (TSC) [65]	Mutation or deletion of *TSC1* (hamartin) or *TSC2* (tuberin) genes, inadequate mTOR suppression and overgrowth (Autosomal dominant)	-Epilepsy in 85 % -IS in 38 % -Seizure onset before 6 months in 46 % -Refractory epilepsy in >50 % Multiple seizure types, focal and generalized	-Developmental delay -Subependymal giant cell astrocytomas (SEGAs) -Cardiac rhabdomyomas
Classic Angelman Syndrome [136]	-Maternal deletion or mutation of 15q11-q13 (68 %) -Uniparental disomy of 15q11-q13 (7 %) -Methylation defect of 15q11-q13 (imprinting error) (2–4 %) -UBE3 mutation or deletion (12 %) (Inheritance pattern varies with defect)	-Epilepsy in 80–95 % -Diagnosis of Angelman often follows diagnosis of seizures -Status epilepticus in 91 % -Seizure onset before 3 years of age -Seizure severity commonly decreases with age -Mostly generalized seizures -Nearly 1/3 with both focal and generalized seizures -IS rare	-Moderate to severe intellectual disability (ID) -Gait ataxia -Peripheral hypertonia -Insomnia -Oubursts of laughter -Fascination with water
Angelman-like Syndromes [137–140]	-*SLC9A6* in Christianson syndrome (X-linked)	-Epilepsy very frequent (~100 %) -Epileptic encephalopathy (>25 %)	-Severe ID -Acquired microcephaly -Cerebellar atrophy -Gastrointenstinal symptoms common
	-*ZEB2* in Mowat-Wilson syndrome	-Epilepsy frequent (70–75 %) -Early onset (<2 years of age) -First seizure typically in context of fever	-Moderate to severe ID -Hypoplasia of corpsus callosum -Hypertelorism +/− telecanthus -Congenital cardiac and renal anomalies -Ophthalmologic abnormalities
	-*TCF4* in Pitt-Hopkins syndrome	-Epilepsy common (40–50 %) -Not well characterized	-Severe ID -Hypotonia -Widely spaced teeth -Less pronounced sleep problems than AS -Breathing abnormalities common
Classic Rett Syndrome [71, 141–144]	-*MECP2* mutation (autosomal dominant), 95 % of cases	-Epilepsy in 80 % -Onset 2–20 years -Variety of seizure types -IS extremely rare -Epilepsy wanes during teenage years	-Acquired microcephaly -Regression of hand use, verbal skills, and gait -Hand stereotypies
Rett Syndrome variants [145–150]	-*STK9/CDKL5* mutations in early seizure variant (X-linked)	-Epilepsy before 6 months of age. -IS +/− hypsarhythmia common -Distinctive seizures: hypermotor-tonic-spasm sequence [151]	-Hypotonia -Cortical visual impairment -Microcephaly -Severe global developmental delay
	-*FOXG1* mutations in congenital variant	-Epilepsy onset variable, 3 months to late childhood -IS not seen -Variable seizure types and severity otherwise -*FOXG1* duplications associated IS but no Rett-like features, seizure onset typically earlier than with deletions	Deletions and intragenic mutations only: -Hypoplastic corpus callosum, simplified gyral pattern, forshortened frontal lobes with reduced white matter volume -Global developmental delay +/− autism -Movement disorder
Ring chromosome 14 [152]		-Epilepsy in 100 %	-Microcephaly

Table 2 (continued)

Syndrome	Gene defect	Epilepsy characteristics	Other clinical features
	Breakage and rejoining of the short and long arms of chromosome 14. (*de novo*)	-Early onset (birth to 2 years) -Multiple seizure types -IS not reported	-Dysmorphic features: epi/telecanthi, broad/flat nasal bridge, large low-set ears -Retinal dystrophy -Developmental delay and intellectual disability
Ring chromosome 20 [153]	Breakage and rejoining of the short and long arms of chromosome 20. (*de novo*)	-Variable phenotype -Severe epilepsy in 90 % -Onset in childhood or adolescent -Most common type is focal frontal lobe seizures (breakpoints concentrated in region of *CHRNA4*, associated with ADFNLE).	-Normal development until seizure onset, then mild to moderate cognitive impairment. -Subtle dysmorphic features
Isodicentric chromosome 15 [154]	Tetrasomy 15q	-Variable phenotype -Onset between 6 months and 9 years -IS common -Benign cases reported	-Early central hypotonia -Developmental delay, intellectual disability
1p36 deletion syndrome [80]	Deletion in the 1p36 region	-Epilepsy in 60 % -Median onset at 3 months -IS+hypsarhythmia in 20 % -Multiple seizure types, focal and generalized	-Craniofacial abnormalities -Congenital heart defects -Precocious puberty -Polymicrogyria common

Treatment is available for a small, but clinically important number of metabolic disorders.

Creatine deficiency syndromes are a spectrum of disorders characterized by epilepsy and developmental delay and can result from mutations in *SLC6A8* on Xq28 (X-linked creatine transporter 1 deficiency), in *GAMT* on 19p13.3 (guanidinoacetate methyltransferase, autosomal recessive), or in *AGAT* on 15q15.3 (arginine:glycine amidinotransferase) [156, 157]. Patients with these mutations may respond to creatine and ornithine supplementation, and therefore, early recognition and confirmation are important.

SLC2A1 mutations can lead to glucose transporter 1 deficiency, which has a phenotype ranging from severe epilepsy in infancy to early-onset absence epilepsy and other primary generalized epilepsies [158]. The diagnosis can be made quickly with measurement of CSF glucose; however, genetic testing may be confirmatory in cases of false positive or negative or borderline glucose measurements and is less invasive than a lumbar puncture in non-acute situations. This gene is clinically important as the mainstay of treatment is ketogenic diet [97]. In addition, the use of valproic acid or phenobarbital can inhibit GLUT1 transport and therefore should be avoided [158].

Pyridoxine-dependent epilepsy is caused by a mutation in the *ALDH7A1* gene, which encodes antiquitin and typically manifests as early-onset epilepsy. It is a highly treatable disorder with timely administration of pyridoxine [159]. Pyridoxal-5-phosphate (P5P) responsive epilepsy is due to mutation in the *PNPO* gene, which leads to pyridoxamine-5-phosphate deficiency. The phenotype is one of a neonatal epileptic encephalopathy. It is thought to be classically responsive to pyridoxal-5-phosphate; however, certain patients respond to pyridoxine instead [27, 28, 151].

Other specific therapies target infantile spasms in tuberous sclerosis complex (TSC), namely vigabatrin [160]. Additionally, mTOR inhibitors are showing early promising results in the treatment of SEGAs in TSC [161]; however, the effect of treatment on seizures is still unknown.

Channelopathies are another area of gene-specific targeting. For instance, anti-seizure medications that block sodium channels in patients with *SCN1A* mutations tend to worsen seizures, and therefore, lamotrigine, phenobarbital, and carbamazepine, for example, are avoided in patients with Dravet syndrome and *SCN1A* mutations [162, 163]. On the other hand, there is anecdotal evidence that patients with *SCN2A* mutation tend to respond better to medications such as lamotrigine and phenobarbital [164]. Ezogabine is a potassium channel opener and has been used in patients with *KCNQ2* mutations, but currently, outcome data is anecdotal. One case report has shown a response to ezogabine in a patient with ring chromosome 20 entailing a *KCNQ2* mutation [165].

A remarkable example of targeted therapy is the use of memantine—an N-methyl-D-aspartate receptor (NMDAR)

blocker—in a patient with epileptic encephalopathy secondary to a *GRIN2A* missense mutation, resulting in meaningful reduction of seizure burden. This mutation resulted in overactivation of NMDARs leading to neuronal excitation and seizures [166•]. Mutations in *GRIN2A*, as discussed before, can result in a range of phenotypes including benign epilepsy with centrotemporal spikes, LKS, and CSWSS, and also epileptic encephalopathy [121, 123, 124, 166•].

Conclusion and Future Directions

Our knowledge of the genetics of the epilepsies has grown exponentially over the past two decades. This has resulted in a great shift in terms of diagnosis and epilepsy classification. The advent of whole-exome sequencing and whole-genome sequencing has improved the detection rates. The use of animal models and patient-derived induced pluripotent cells for functional analysis of genetic mutations has been key in understanding the pathophysiology and mechanisms of many of the epilepsies. There is still, however, much future work to be done.

In terms of diagnostics, the use of more advanced testing including deep sequencing and single cell sequencing has started but is not readily available. Functional analysis remains confined to research laboratories, and the hope is that in the future, it will become more readily available as a clinical tool for better understanding of unique and individual mutations.

Targeted treatment of genetic epilepsies will continue to depend on the available knowledge of the molecular mechanisms and pathophysiology, and also on further targeted drug development.

And, last but not least, collaboration between clinicians across institutions is essential to further our knowledge in epilepsy genetics, particularly as we move to provide not only more precise genetic diagnoses but also eventually genetically informed treatments.

Compliance with Ethics Guidelines

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