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Genetic Basis of Early-onset Developmental and Epileptic Encephalopathies

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Developmental and epileptic encephalopathies are the most devastating early-onset epilepsies, characterized by early-onset seizures that are often intractable, electroencephalographic abnormalities, developmental delay or regression, and various comorbidities. A large number of underlying genetic variants of developmental and epileptic encephalopathies have been identified over the past few decades. However, the most thorough sequencing studies leave 60–65% of patients without a molecular diagnosis. This review explores the genetic basis of developmental and epileptic encephalopathies that start within the first year of life, including Ohtahara syndrome, early myoclonic encephalopathy, epilepsy of infancy with migrating focal seizures, infantile spasms, and Dravet syndrome. The purpose of this review is to give an overview and encourage the clinicians to start considering genetic testing as an important investigation along with electroencephalogram for better understanding and management of developmental and epileptic encephalopathies.

Key words: Early-onset epileptic encephalopathy, Infants, Genetics, Developmental and epileptic encephalopathies

REVIEW ARTICLE

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INTRODUCTION

Developmental and epileptic encephalopathies (DEEs) are a rare heterogeneous group of neurodevelopmental disorders, characterized by early-onset seizures that are often intractable, electroencephalographic abnormalities, developmental delay or regression, and various comorbidities [1-3]. Previous studies showed that one-third of children presenting with epilepsy before the age of three are medically intractable and 36% of epilepsy beginning before the age of two manifest as epileptic encephalopathy [4,5]. A growing number of genetically determined forms of DEEs have been identified over the past few decades [6]. The underlying genetic etiology is not only associated with frequent epileptic activity but also with a developmental delay because their onset coincides with crucial neurodevelopment [6,7]. Large-scale research has been uncovering numerous genes associated with DEEs, using chromosomal microarrays, whole exome sequencing (WES) and whole genome sequencing (WGS) [8,9]. However, the most thorough sequencing studies leave 60–65% of patients without a molecular diagnosis [9]. In contrast, in smaller studies of neonates and infants with epileptic encephalopathy, 80% or more of the patients had a genetic cause [10,11], which implicates the importance of patient selection and diagnostic methods. Here, we reviewed causative genes for early-onset DEEs including Ohtahara syndrome, early myoclonic encephalopathy (EME), epilepsy of infancy with migrating focal seizures (EIMFS), infantile spasms (West syndrome), and Dravet syndrome that start within the first year of life. The purpose of this review is to help increase recognition of early-onset DEEs and encourage the clinicians to start considering genetic testing as an important investigation along with an electroencephalogram for bet-

ter understanding and management of DEEs.

AVAILABLE GENETIC TESTING AND DIAGNOSTIC YIELD

The first recognition of a genetic cause for an epileptic encephalopathy was in 2001, with the finding of de novo *SCN1A* variants in Dravet syndrome patients [12]. Genetic testing for DEEs includes karyotype, chromosomal microarray (CMA), single-gene sequencing, panel sequencing, whole exome sequencing, and whole genome sequencing. Karyotype may be useful in cases with dysmorphism, multi-organ involvement, and epilepsy and can help to identify rearrangements such as translocations, aneuploidy, or ring chromosome [13,14]. Diagnostic yield of karyotype remains unclear in DEEs. Copy number variation is an important molecular cause of epileptic encephalopathy, with the diagnostic yield from chromosomal microarray ranges from 5% to 16% [15-17]. Single gene sequencing may be useful when the phenotype suggests a specific syndrome such as Dravet syndrome, tuberous sclerosis complex, or GLUT-1 transporter defect [13,14]. The diagnostic yield of single gene sequencing depends on genes tested. When the clinical presentation is undifferentiated and there is phenotypic variability, gene panels and whole exome sequencing are the preferred and more efficient tools than single gene sequencing [6]. Gene panels may allow for the sequencing of hundreds of genes at once via next-generation sequencing, and their overall yield is between 15% and 25% in epileptic encephalopathies [14,18]. The number of genes included in gene panels ranges from 38 to 327, and whether including more genes would increase the yield of gene sequencing remains unclear, as 93% of genetically diagnosed patients were identified using 38-gene panels [19]. When whole exome sequencing is performed early in diagnostic evaluation in conjunction with trio-testing, diagnostic yield ranges from 20% to 40% [13,14,18].

CAUSATIVE GENES FOR DEES

Table 1 summarizes the phenotype MIM number, gene, location, inheritance, and protein function for DEEs. Several studies uncovered the pathogenic role of genetic variants involved in the synaptogenesis, pruning, neuronal migration and differentiation, neurotransmitter synthesis and release, structures, and functions of membrane receptors and transporters [20,21]. In a recent study of 41 infantile-onset DEE patients, the seven most frequent pathogenic or likely pathogenic variants were *KCNQ2*, *STXBP1*, *CDKL5*, *SCN1A*, *KCNT1*, *SCN2A*, and *SCN8A* [22]. In another study of 105 patients with epileptic encephalopathy who underwent genetic testing using the Illumina TruSight One panel, a diagnostic panel of 47 epileptic encephalopathy genes, 30 out of 105 patients (28.5%) were identified with pathogenic variants and likely pathogenic variants in *ALDH7A1*, *CACNA1A*, *CDKL5*, *FOXG1*, *GABRB3*, *GRIN2A*, *KCNQ2*, *KCNQ3*, *PRRT2*, *SCN1A*, *SCN2A*, *SCN8A*, *SYNGAP1*, *UBE3A*, and *WWOX* [23]. In another study of the 68 infants with epileptic encephalopathy, 13 patients (19%) were identified with pathogenic variants in 7 genes; SCN1A was the most frequently affected gene accounting for 38.5%, followed by *STXBP1* (15.4%), *CDKL5* (15.4%), *KCNQ2* (15.4%), *ARX* (7.7%), and *SCN8A* (7.7%) [24].

ELECTROCLINICAL CHARACTERISTICS AND GENETIC ETIOLOGIES OF DEES

Ohtahara syndrome or early infantile epileptic encephalopathy with suppression-burst pattern is age-dependent epileptic encephalopathy that usually occurs within the first 3 months of age [20,25]. The most typical seizures are tonic spasms with or without series formation, although other seizure types can also be observed [20,26]. Electroencephalogram (EEG) shows a continuous suppression-burst pattern, higher-voltage bursts of slow waves mixed with multifocal spikes and alternate with isoelectric suppression phase in both waking and sleeping states [27]. Seizure patterns usually change with age, frequently evolve to West syndrome and further to Lennox-Gastaut syndrome [28]. The most frequent genetic abnormalities are found in *STXBP1* (~30%), *KCNQ2* (~20%), *SCN2A* (~10%); less common genetic variants are found in AARS, *ARX*, *BRAT1*, *CACNA2D2*, *GNAO1*, *KCNT1*, *NECAP1*, *PIGA*, *PIGQ*, *SCN8A*, *SIK1*, *GABRA1*, and *SLC25A22* [29,30].

Early myoclonic encephalopathy

EME occurs within the first 3 months of age. Seizures are characterized by fragmentary myoclonic jerks which shift typically from one part of the body to another in a random, asynchronous pattern; other seizure types including tonic and focal seizures may also be observed [29-31]. Typical EEG shows a suppression-burst pattern like that seen in Ohtahara syndrome which becomes more prominent in sleep and may evolve to hypsarrhythmia in the middle to late infancy [25,32]. EME persists for long periods without evolution, except for the occasional transient phase of West syndrome, or changes into

Table 1. Summary of genes and protein functions for developmental and epileptic encephalopathies

Type	Phenotype MIM number	Gene	Location	Inheritance	Protein function
DEE1	308350	ARX	Xp21.3	XLR	Transcriptional repressor and activator
DEE2	300672	CDKL5	Xp22.13	XLD	Serine-threonine kinase
DEE3	609304	SLC25A22	11p15.5	AR	Transport of glutamate across the inner mitochondrial membrane
DEE4	612164	STXBP1	9q34.11	AD	Modulator of synaptic vesicle release
DEE5	613477	SPTAN1	9q34.11	AD	Cytoskeletal protein
DEE6	607208	SCN1A	2q24.3	AD	Subunit of a voltage-gated sodium channel
DEE7	613720	KCNQ2	20q13.33	AD	Subunit of a voltage-gated potassium channel
DEE8	300607	ARHGEF9	Xq11.1	XLR	Rho-like GTPase to regulate CDC42 and other genes
DEE9	300088	PCDH19	Xq22.1	XL	calcium-dependent cell-adhesion protein
DEE10	613402	PNKP	19q13.33	AR	Enzyme involved in DNA repair
DEE11	613721	SCN2A	2q24.3	AD	Subunit of a voltage-gated sodium channel
DEE12	613722	PLCB1	20p12.3	AR	Mediates intracellular signaling downstream of G protein-coupled receptors and regulates the function of the endothelial barrier
DEE13	614558	SCN8A	12q13.13	AD	Subunit of a voltage-gated sodium channel
DEE14	614959	KCNT1	9q34.3	AD	Subunit of a sodium-activated potassium channel
DEE15	615006	ST3GAL3	1p34.1	AR	Catalyzes the transfer of sialic acid from CMP-sialic acid to galactose-containing substrates
DEE16	615338	TBC1D24	16p13.3	AR	GTPase-activating protein for Rab family protein
DEE17	615473	GNAO1	16q13	AD	Modulators or transducers in various transmembrane signaling systems
DEE18	615476	SZT2	1p34.2	AR	Localized to the peroxisome, and is implicated in resistance to oxidative stress
DEE19	615744	GABRA1	5q34	AD	A component of the heteropentameric receptor for GABA
DEE20	300868	PIGA	Xp22.2	XLR	Catalytic subunit of the glycosylphosphatidylinositol-N-acetylglucosaminyltransferase complex
DEE21	615833	NECAP1	12p13.31	AR	Involved in endocytosis
DEE22	300896	SLC35A2	Xp11.23	SMo, XLD	Transports nucleotide sugars from the cytosol into Golgi vesicles where glycosyltransferases function
DEE23	615859	DOCK7	1p31.3	AR	Functions as a guanine nucleotide exchange factor, which activates Rac1 and Rac3 Rho small GTPases by exchanging bound GDP for free GTP
DEE24	615871	HCN1	5p12	AD	Hyperpolarization-activated ion channel exhibiting weak selectivity for potassium over sodium ions
DEE25	615905	SLC13A5	17p13.1	AR	High-affinity sodium/citrate cotransporter that mediates citrate entry into cells and facilitate the synthesis of fatty acids and cholesterol
DEE26	616056	KCNB1	20q13.13	AD	Voltage-gated potassium channel that mediates transmembrane potassium transport in excitable membranes, primarily in the brain, but also in the pancreas and cardiovascular system
DEE27	616139	GRIN2B	12p13.1	AD	Component of NMDA receptor complexes that function as heterotetrameric, ligand-gated ion channels with high calcium permeability and voltage-dependent sensitivity to magnesium
DEE28	616211	WWOX	16q23.1-q23.2	AR	Acts as a tumor suppressor and plays a role in apoptosis
DEE29	616339	AARS1	16q22.1	AR	Catalyzes the attachment of alanine to tRNA in a two-step reaction: alanine is first activated by ATP to form Ala-AMP and then transferred to the acceptor end of tRNA
DEE30	616341	SIK1	21q22.3	AD	Serine/threonine-protein kinase involved in various processes such as cell cycle regulation, gluconeogenesis and lipogenesis regulation, muscle growth and differentiation and tumor suppression

(*Continued to the next page*)

Table 1. Continued

Type	Phenotype MIM number	Gene	Location	Inheritance	Protein function
DEE31	616346	DNM1	9q34.11	AD	Microtubule-associated force-producing protein involved in producing microtubule bundles and able to bind and hydrolyze GTP
DEE32	616366	KCNA2	1p13.3	AD	Voltage-gated potassium channel that mediates transmembrane potassium transport in excitable membranes, primarily in the brain and the central nervous system, but also in the cardiovascular system
DEE33	616409	EEF1A2	20q13.33	AD	Promotes the GTP-dependent binding of aminoacyl-tRNA to the A-site of ribosomes during protein biosynthesis
DEE34	616645	SLC12A5	20q13.12	AR	Mediates electroneutral potassium-chloride cotransport in mature neurons and is required for neuronal Cl- homeostasis
DEE35	616647	ITPA	20p13	AR	Pyrophosphatase that hydrolyzes the non-canonical purine nucleotides inosine triphosphate, deoxyinosine triphosphate as well as 2'-deoxy-N-6-hydroxylaminopurine triposphate and xanthosine 5'-triphosphate to their respective monophosphate derivatives
DEE36	300884	ALG13	Xq23	XL	Multifunctional enzyme with both glycosyltransferase and deubiquitinase activities
DEE37	616981	FRRS1L	9q31.3	AR	Important modulator of glutamate signaling pathway
DEE38	617020	ARV1	1q42.2	AR	Plays a role as a mediator in the endoplasmic reticulum cholesterol and bile acid homeostasis
DEE39	612949	SLC25A12	2q31.1	AR	Mitochondrial and calcium-binding carrier that catalyzes the calcium-dependent exchange of cytoplasmic glutamate with mitochondrial aspartate across the mitochondrial inner membrane
DEE40	617065	GUF1	4p12	AR	Promotes mitochondrial protein synthesis and may act as a fidelity factor of the translation reaction, by catalyzing a one-codon backward translocation of tRNAs on improperly translocated ribosomes
DEE41	617105	SLC1A2	11p13	AD	Sodium-dependent, high-affinity amino acid transporter that mediates the uptake of L-glutamate and also L-aspartate and D-aspartate
DEE42	617106	CACNA1A	19p13.13	AD	Voltage-sensitive calcium channels that mediate the entry of calcium ions into excitable cells and are also involved in a variety of calcium-dependent processes, including muscle contraction, hormone or neurotransmitter release, gene expression, cell motility, cell division and cell death
DEE43	617113	GABRB3	15q12	AD	Ligand-gated chloride channel which is a component of the heteropentameric receptor for GABA, the major inhibitory neurotransmitter in the brain
DEE44	617132	UBA5	3q22.1	AR	E1-like enzyme which specifically catalyzes the first step in ufmylation
DEE45	617153	GABRB1	4p12	AD	Component of the heteropentameric receptor for GABA, the major inhibitory neurotransmitter in the vertebrate brain
DEE46	617162	GRIN2D	19q13.33	AD	Component of NMDA receptor complexes that function as heterotetrameric, ligand-gated ion channels with high calcium permeability and voltage-dependent sensitivity to magnesium
DEE47	617166	FGF12	3q28-q29	AD	Involved in nervous system development and function and promotes neuronal excitability by elevating the voltage dependence of neuronal sodium channel SCN8A fast inactivation
DEE48	617276	AP3B2	15q25.2	AR	Subunit of non-clathrin- and clathrin-associated adaptor protein complex 3 that plays a role in protein sorting in the late-Golgi/trans-Golgi network and/or endosomes
DEE49	617281	DENND5A	11p15.4	AR	Promotes the exchange of GDP to GTP, converting inactive GDP-bound Rab proteins into their active GTP-bound form
DEE50	616457	CAD	2p23.3	AR	Encodes four enzymatic activities of the pyrimidine pathway (GATase, CPSase, ATCase and DHOase)
DEE51	617339	MDH2	7q11.23	AR	Malate dehydrogenase, mitochondrial
DEE52	617350	SCN1B	19q13.11	AR	Regulatory subunit of multiple voltage-gated sodium channel complexes that play important roles in excitable membranes in brain, heart and skeletal muscle
DEE53	617389	SYNJ1	21q22.11	AR	Phosphatase that acts on various phosphoinositides, including phosphatidylinositol 4-phosphate, phosphatidylinositol (4,5)-bisphosphate and phosphatidylinositol (3,4,5)-trisphosphate
DEE54	617391	HNRNPU	1q44	AD	DNA- and RNA-binding protein involved in several cellular processes such as nuclear chromatin organization, telomere-length regulation, transcription, mRNA alternative splicing and stability, Xist-mediated transcriptional silencing and mitotic cell progression
DEE55	617599	PIGP	21q22.13	AR	Part of the glycosylphosphatidylinositol-N-acetylglucosaminyltransferase (GPI-GnT) complex that catalyzes the transfer of N-acetylglucosamine from UDP-N-acetylglucosamine to phosphatidylinositol and participates in the first step of GPI biosynthesis
DEE56	617665	YWHAG	7q11.23	AD	Adapter protein implicated in the regulation of a large spectrum of both general and specialized signaling pathways

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Table 1. Continued

Type	Phenotype MIM number	Gene	Location	Inheritance	Protein function
DEE57	617771	KCNT2	1q31.3	AD	Outward rectifying potassium channel which produces rapidly activating outward rectifier K+ currents
DEE58	617830	NTRK2	9q21.33	AD	Receptor tyrosine kinase involved in the development and the maturation of the central and the peripheral nervous systems through regulation of neuron survival, proliferation, migration, differentiation, and synapse formation and plasticity
DEE59	617904	GABBR2	9q22.33	AD	Component of a heterodimeric G-protein coupled receptor for GABA, formed by GABBR1 and GABBR2
DEE60	617929	CNPY3	6p21.1	AR	Toll-like receptor (TLR)-specific co-chaperone for HSP90B1. Required for proper TLR folding, except that of TLR3, and hence controls TLR exit from the endoplasmic reticulum
DEE61	617933	ADAM22	7q21.12	AR	Probable ligand for integrin in the brain, involved in regulation of cell adhesion and spreading and in inhibition of cell proliferation
DEE62	617938	SCN3A	2q24.3	AD	Mediates the voltage-dependent sodium ion permeability of excitable membranes
DEE63	617976	CPLX1	4p16.3	AR	Positively regulates a late step in exocytosis of various cytoplasmic vesicles, such as synaptic vesicles and other secretory vesicles
DEE64	618004	RHOBTB2	8p21.3	AD	Interacts with the cullin-3 protein, a ubiquitin E3 ligase necessary for mitotic cell division
DEE65	618008	CYFIP2	5q33.3	AD	Involved in T-cell adhesion and p53/TP53-dependent induction of apoptosis
DEE66	618067	PACS2	14q32.33	AD	Multifunctional sorting protein that controls the endoplasmic reticulum (ER)-mitochondria communication, including the apposition of mitochondria with the ER and ER homeostasis
DEE67	618141	CUX2	12q24.11-q24.12	AD	Transcription factor involved in the control of neuronal proliferation and differentiation in the brain and regulates dendrite development and branching, dendritic spine formation, and synaptogenesis in cortical layers II-III
DEE68	618201	TRAK1	3p22.1	AR	Involved in the regulation of endosome-to-lysosome trafficking, including endocytic trafficking of EGF-EGFR complexes and GABA-A receptors
DEE69	618285	CACNA1E	1q25.3	AD	Voltage-sensitive calcium channels mediate the entry of calcium ions into excitable cells
DEE70	618298	PHACTR1	6p24.1	AD	Binds actin monomers (G actin) and plays a role in multiple processes including the regulation of actin cytoskeleton dynamics, actin stress fibers formation, cell motility and survival, formation of tubules by endothelial cells, and regulation of PPP1CA activity
DEE71	618328	GLS	2q32.2	AR	Catalyzes the first reaction in the primary pathway for the renal catabolism of glutamine and regulates the levels of the neurotransmitter glutamate, the main excitatory neurotransmitter in the brain
DEE72	618374	NEUROD2	17q12	AD	Critical factor essential for the repression of the genetic program for neuronal differentiation; prevents the formation of synaptic vesicle clustering at active zone to the presynaptic membrane in postmitotic neurons
DEE73	618379	RNF13	3q25.1	AD	Plays a role in cell proliferation, apoptosis regulation, and mediates ER stress-induced activation of JNK signaling pathway and apoptosis by promoting ERN1 activation and splicing of XBP1 mRNA
DEE74	618396	GABRG2	5q34	AD	Ligand-gated chloride channel which is a component of the heteropentameric receptor for GABA, the major inhibitory neurotransmitter in the brain
DEE75	618437	PARS2	1p32.3	AR	Encodes a putative member of the class II family of aminoacyl-tRNA synthetases and plays a critical role in protein biosynthesis by charging tRNAs with their cognate amino acids
DEE76	618468	ACTL6B	7q22.1	AR	Involved in transcriptional activation and repression of select genes by chromatin remodeling
DEE77	618548	PIGQ	16p13.3	AR	Part of the glycosylphosphatidylinositol-N-acetylglucosaminyltransferase (GPI-GnT) complex that catalyzes the transfer of N-acetylglucosamine from UDP-N-acetylglucosamine to phosphatidylinositol and participates in the first step of GPI biosynthesis
DEE78	618557	GABRA2	4p12	AR	Ligand-gated chloride channel which is a component of the heteropentameric receptor for GABA, the major inhibitory neurotransmitter in the brain
DEE79	618559	GABRA5	15q12	AD	Ligand-gated chloride channel subunit which is a component of the heteropentameric receptor for GABA, the major inhibitory neurotransmitter in the brain
DEE80	618580	PIGB	15q21.3	AR	Involves in glycosylphosphatidylinositol-anchor biosynthesis and transfers the third alpha-1,2-mannose to Man2-GlcN-acyl-PI during GPI precursor assembly

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Table 1. Continued

Type	Phenotype MIM number	Gene	Location	Inheritance	Protein function
DEE81	618663	DMXL2	15q21.2	AR	Serves as a scaffold protein for MADD and RAB3GA on synaptic vesicles and plays a role in the brain as a key controller of neuronal and endocrine homeostatic processes
DEE82	618721	GOT2	16q21	AR	Catalyzes the irreversible transamination of the L-tryptophan metabolite L-kynurenine to form kynurenic acid
DEE83	618744	UGP2	2p15	AR	Catalyzes the glucose-1-phosphate into UDP-glucose, a crucial precursor for the production of glycogen
DEE84	618792	UGDH	4p14	AR	Catalyzes the formation of UDP-alpha-D-glucuronate, a constituent of complex glycosaminoglycans
DEE85	301044	SMC1A	Xp11.22	XLD	Involved in chromosome cohesion during cell cycle and in DNA repair
DEE86	618910	DALRD3	3p21.31	AR	A tRNA-binding protein that interacts with the methyltransferase METTL2 and facilitates METTL2-catalyzed m3C formation at position 32 in specific arginine tRNAs
DEE87	618916	CDK19	6q21	AD	In conjunction with its paralog CDK8 and other proteins, form a CDK module which regulates RNA polymerase II and transcriptional activity
DEE88	618959	MDH1	2p15	AR	Plays essential roles in the malate-aspartate shuttle and the tricarboxylic acid cycle, important in mitochondrial NADH supply for oxidative phosphorylation
DEE89	619124	GAD1	2q31.1	AR	Catalyzes the production of GABA
DEE90	301058	FGF13	Xq26.3-q27.1	XLD	Microtubule-binding protein which directly binds tubulin and is involved in both polymerization and stabilization of microtubules

AD, autosomal dominant; AR, autosomal recessive; XL, X-linked; XLD, X-linked dominant; XLR, X-linked recessive; SMo, somatic mosaicism.

partial or severe epilepsy with multiple independent spike foci [25]. EME usually associated with inherited metabolic disorders, such as nonketotic hyperglycinemia, organic acidemias, Zellweger syndrome, and molybdenum cofactor deficiency [33]. In patients presenting as EME with negative metabolic workup, the most common genetic variants are found in *ERBB4*, *PIGA*, *SETBP1*, *SIK1*, and *SLC25A22* [30].

Epilepsy of infancy with migrating focal seizures

EIMFS begins within the first 6 months of life. Migrating focal seizures occur usually in clusters lasting a few days followed by a few weeks or months of recovery. Seizures are very frequent within a cluster, and clusters increase in frequency within the first 2 years of life. EEG is usually normal at onset; spikes rapidly grow in frequency and develop multifocal within a few months. Multifocal spike-and-wave activities do not show any specific pattern and are not activated in sleep. The ictal EEG pattern is characterized by rhythmic monomorphic activity in the alpha-theta frequency range, although, spikes, and spike-waves can also be observed. It is common for an epileptic activity to remain limited to one region for a period of time and then progressively involve an adjacent area [34]. De novo *KCNT1* variants (~50%) and *SCN2A* (~25%); less frequent genetic variants have been reported in *PLCB1*, *QARS*, *SCN1A*, *SCN8A*, *SLC25A22*, *TBC1D24*, and *SLC12A5* [30,35-37].

Infantile spasms (West syndrome)

Infantile spasms or West syndrome is the most common epilepsy syndrome in infancy that usually starts in the first year of life, most frequently between the first 3 and 9 months of life. Infantile spasms represent a combination of the triad of infantile spasms, developmental deterioration, and hypsarrhythmic EEG pattern [38,39]. Seizures are characterized by brief symmetrical contractions of proximal and truncal muscles, which frequently occur in clusters [40,41]. Hypsarrhythmia, a typical interictal EEG pattern, consists of high amplitude, disorganized, and chaotic pattern with multifocal spikes and sharp wave discharges [29]. Ictal EEG activity includes a diffuse high-amplitude triphasic slow wave, a low-amplitude brief fast discharge, or a short-lasting diffuse flattening of ongoing activity [42,43]. Genetic variants have been reported in *CDKL5* (~10%), *STXBP1* (~2%), *ARX*, *GAMT*, *ALG13*, *SCN2A*, *SCN1A*, *ALG13*, *GABRB3*, *GNAO1*, *GRIN1*, *GRIN2A*, *GRIN2B*, *DNM1*, *DOCK7*, *FOXG1* (duplications), *SCN8A*, *MAGI2*, *MEF2C*, *NEDDL4*, *NDP*, *NRXN1*, *ACADS*, *WDR45*, *PIGA*, *PLCB1*, *PTEN*, *SCA2*, *SCN1A*, *SETBP1*, *SIK1*, *SLC25A22*, *SLC35A2*, *SPTAN1*, *ST3Gal3*,

TBC1D24, *TCF4*, *WWOX*, and *GABRA1* [30,44,45].

Dravet syndrome

Dravet syndrome is a severe epileptic encephalopathy, which begins in the first year of life in a previously healthy infant. Seizures are unilateral or generalized clonic or tonic-clonic, which are commonly prolonged and could be progressed into status epilepticus. Seizures are usually triggered by fever, immunization, or a hot environment but may also be afebrile [46]. During the second year of life, seizures no longer occur only when a child has a high temperature, and become more frequent, persistent, and often more lateralized [31]. EEG shows generalized focal and multifocal abnormalities, spikes, and spike-wave or polyspike-wave discharges, symmetric or not, predominate over the frontal and central areas, but occur over the temporal and occipital areas, too [47,48]. Channelopathy due to variants in the *SCN1A* gene encoding the alpha 1 subunit of the voltage-gated sodium (Nav1.1) channel has been reported in 90% of patients, with most de novo and missense variants. Less frequent genetic variants are found in *PCDH19*, *GABRA1*, *GABRG2*, *HCN1*, and *STXBP1* [1,30,49]. *SCN1A* variants have been observed in a spectrum of febrile epilepsy syndromes, which ranges from genetic epilepsy with febrile seizures plus (GEFS+) to Dravet syndrome.

DISCUSSION

With shortened time and decrease in cost, next-generation sequencing has provided earlier diagnosis and earlier appropriate treatment in patients with DEEs, especially in those patients where clinical symptoms are not well-defined. Despite the increased genetic diagnostic yield, still, a considerable number of the patients remain undiagnosed. Medically intractable seizures and severe developmental delay are all the more frustrating when the genetic cause remains unknown. And thus, discovering the genetic etiology of DEEs has been the code to be deciphered for pediatric neurologists. Future directions to increase the diagnostic yield may include whole genome sequencing, targeted sequencing panels with single-molecule molecular inversion probes (smMIP), and possibly brain tissue transcriptome analysis with total RNA sequencing. Identification of further genes and novel pathways will provide a clear picture to families and caregivers and may also help in the development of target-specific therapies in DEEs.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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