Association between phenotypes and genotype of developmental and epileptic encephalopathy in next-generation sequencing methods in infants: A scoping review

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ABSTRACT

Introduction: Developmental and epileptic encephalopathy (DEE) is epilepsy related to developmental impairment that may be caused by both the underlying etiology (developmental encephalopathy) and superimposed epileptic activity (epileptic encephalopathy). The origin of DEE and the causes of its variations remain unknown. Owing the lack of clarity regarding the role of genetic variables in DEE, we conducted a scoping review to qualitatively identify the genes most important in the development of DEE to provide an up-to-date review.

Material and methods: We searched all published studies related to the genetic factors of DEE. The identified publications were screened and selected by the authors on basis of on inclusion and exclusion criteria and assessed for methodological quality. Eighteen articles were included. The extracted data included age of onset, sex, gene mutations and inheritance (e.g. nucleotide change, protein change, and family testing), clinical manifestation, electroencephalogram, imaging, medication, and outcomes.

Result: A total of 18 studies were included in this scoping review. The most frequently reported gene variants were STXBP1 in Ohtahara Syndrome, SLC1A2 in Early Myoclonic Encephalopathy (EME), CDKL5 in West Syndrome, SCN1A in Dravet Syndrome, and KCNT1 in Epilepsy of Infancy with Migrating Focal Seizures (EIMFS). Each gene was associated with distinct electroclinical features, including differences in age of onset, seizure type, EEG patterns, and developmental outcomes. While genotype and phenotype associations were heterogeneous, certain variants showed consistent patterns indicative of more severe disease courses.

Conclusions: This review identified key gene variants commonly associated with early-onset DEE in infants, particularly STXBP1, SLC1A2, CDKL5, SCN1A, and KCNT1, each linked to unique clinical presentations and outcomes. These findings support the clinical utility of next-generation sequencing (NGS) for early diagnosis and tailored treatment planning in DEE. Understanding genotype–phenotype correlations may enhance prognostication and highlight potential avenues for targeted therapy in future research.

KEYWORDS:
Developmental and epileptic encephalopathy; infant; genetic; scoping review

INTRODUCTION

International League Against Epilepsy (ILAE) proposed the term developmental and epileptic encephalopathy (DEE) in "2017 Classification of the Epilepsies" to describe epilepsy related to developmental impairment that may be caused by both the underlying etiology (developmental encephalopathy) and superimposed epileptic activity (epileptic encephalopathy).[1]

Epilepsy incidence generally varies according to age, with younger children and individuals aged 65 years or older experiencing the highest frequencies (>60 per 100,000) individuals. Several population-based studies reported that younger children experience epilepsy at considerably higher rates than older children (82.1–118 vs. 46 per 100,000 person-years). Zuberi et al. reported that neonatal and infant epilepsy syndromes can be broadly categorized into the following two groups: self-limited epilepsies (where there is a decent possibility of spontaneous remission) and DEE.[2] In the newest classification of epilepsy, which is defined by ILAE, syndromes with developmental and/or epileptic encephalopathy or with progressive neurological deterioration were combined, subsequently, the categories were divided by the age of onset.[3–5]

Recent studies have shown that genetic causes have been identified in different epileptic encephalopathies, and various previously unknown genes have appeared.[6] Several of these syndromes are associated with genetic etiology. Development in genomics technology, including next-generation sequencing, has allowed us to discover genes involved in various disorders.[6,7] Genetic testing has proven instrumental

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in improving diagnostic yield, informing treatment decisions, and guiding genetic counseling.

Despite these advances, a comprehensive synthesis of the genetic landscape of DEE in infants, especially regarding genotype-phenotype correlations remains lacking. This gap underscores the need for a scoping review that systematically maps current evidence on the genetic etiology of DEE in this age group.

This review aims to answer the following research question: Which gene mutations have been most frequently reported in infants with DEE, and what are the associated clinical phenotypes and inheritance patterns. Accordingly, the objective of this scoping review is to identify and summarize the most commonly reported genetic variants associated with DEE in infants, based on studies utilizing next-generation sequencing technologies.

MATERIALS AND METHODS

Protocol registration

This scoping review protocol was not prospectively registered. Although prospective registration is increasingly encouraged to promote transparency and minimize bias, the review was developed and conducted prior to formal registration. Nevertheless, all methodological steps followed established scoping review frameworks to ensure rigor and reproducibility.

Search strategy

A comprehensive search was conducted across multiple databases, including Cochrane, PubMed, BMC, BMJ, ScienceDirect, EBSCOhost, ProQuest, Google Scholar, and Sage Journals, up to August 2022. Search terms were selected to capture relevant studies on the genotype-phenotype relationships in developmental and epileptic encephalopathies (DEE). These terms were grouped into disease-related and diagnostic method-related categories.

a) Disease-related terms included:
"epileptic encephalopathy", "early onset epileptic encephalopathy", "Ohtahara syndrome", "early myoclonic epilepsy", "epilepsy in infancy with migrating focal seizure", "West syndrome", "infantile spasm", "Dravet syndrome".
b) Diagnostic method-related terms included:
"genetic testing", "next-generation sequencing", "gene panel", "whole exome sequencing", and "whole genome sequencing".

The terms were combined using Boolean operators (AND/OR) to ensure comprehensive coverage of relevant studies. For example, the search string for PubMed was as follows:
("epileptic encephalopathy" OR "early onset epileptic encephalopathy" OR "Ohtahara syndrome" OR "early myoclonic epilepsy" OR "epilepsy in infancy with migrating focal seizure" OR "West syndrome" OR "infantile spasm" OR "Dravet syndrome") AND ("genetic testing" OR "next-generation sequencing" OR "gene panel" OR "whole exome sequencing" OR "whole genome sequencing").

Eligibility criteria

Research articles were selected and published between 2012 and 2022. To ensure the validity of the search strategy, all research articles included in our scoping review were assessed with inclusion and exclusion criteria. Observational studies, such as case-control, cross-sectional, and cohort studies, were included in this study. Self-reported surveys, reviews, case reports, case series, editorials, commentaries, and expert opinions were excluded. All participants had to meet the following criteria: age of onset between 0-18 years (pediatric patients), and genetic diagnostic methods used were either whole exome sequencing (WES), whole genome sequencing (WGS), or multiple gene panels performed on more than 50 genes. Moreover, the articles had to specifically identify gene mutation-related DEE. Articles that were not written in English and studies that excluded data taken from human beings were also excluded.

PRISMA-ScR Checklist

To improve the quality and transparency of scoping reviews, we followed the PRISMA-ScR checklist, which is available in the Supplementary Materials. This checklist was completed and included as Supplementary Material to ensure adherence to reporting standards and to help readers assess the completeness of the review process.

Data analysis

Mendeley software was used to identify duplicate records and facilitate assist in the screening of titles, abstracts, and full texts based on predefined inclusion and exclusion criteria. The primary reviewer (AT) and additional reviewers (ESH and G) conducted the article screening and selection. Data validation was performed collaboratively by all reviewers, with additional assistance from KHM and KI. Any disagreements were resolved through discussion

The extracted data included patient characteristics (such as age of onset and sex), genetic findings (including gene mutations, inheritance patterns, nucleotide and protein changes, and results of family testing), clinical features, EEG findings, neuroimaging results, treatments, and outcomes.

As this is a scoping review, a formal quality assessment of included studies was not conducted. The aim was to map the current evidence and highlight key areas for future research, clinical guidance, and policy development,

RESULTS

Study characteristics

A total of 8,414 records were identified through database searching. After duplicate records were eliminated, 8,303 records. Next, following title and abstract screening, 7,893 records were eliminated. The eligibility of 410 full-text entries was evaluated in accordance with the inclusion/exclusion criteria. Finally, 18 distinct studies were included in this analysis following the exclusion of 32 full-text articles owing to various reasons indicated in the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) flow diagram in Fig. 1

Table I: Papers included in scoping review

No.	Author	Title	Year	Study type	Sample size	Genetic test
1	Costain, et al.[32]	Clinical Application of Targeted Next-Generation Sequencing Panels and Whole Exome Sequencing in Childhood Epilepsy	2019	Retrospective cohort study	197	WES and TNGS (189 genes)
2	Myers,et al.[33]	De Novo Mutations in SLC1A2 and CACNA1A are Important Causes of Epileptic Encephalopathies	2016	Cohort	531	Targeted sequencing (290 genes)
3	Kothur, et al.[4]	Diagnostic yield of targeted massively parallel sequencing in children with epileptic encephalopathy.	2017	Cohort	141	Targeted panel 71 genes
4	Carvill, et al.[34]	GABRA1 and STXBP1: novel genetic causes of Dravet syndrome.	2014	Cohort	67	WES
5	Komulainen-Ebrahim, et al.[6]	Genetic Aetiologies and Phenotypic Variations of Childhood-Onset Epileptic Encephalopathies and Movement Disorders	2019	Cross sectional	12	WES
6	Wang, et al.[7]	Genetic Variants Identified from Epilepsy of Unknown Etiology in Chinese Children by Targeted Exome Sequencing.	2020	Retrospective cohort study	63	Targeted panel (412 genes)
7	Hino-Fukuyo, et al.[35]	Genomic analysis identifies candidate pathogenic variants in 9 of 18 patients with unexplained West syndrome.	2015	Cohort	18	WES
8	Mitta, et al.[27]	Genotype-phenotype correlates of infantile-onset developmental & epileptic encephalopathy syndromes in South India: A single centre experience.	2020	Retrospective cohort study	82	Multiple gene panel
9	Kobayashi, et al.[36]	High prevalence of genetic alterations in early-onset epileptic encephalopathies associated with infantile movement disorders.	2016	Cohort	11	WES
10	Hamdan, et al.[37]	High Rate of Recurrent De Novo Mutations in Developmental and Epileptic Encephalopathies	2017	Cohort	197	WGS
11	Zhou, P et al.[29]	Novel mutations and phenotypes of epilepsy-associated genes in epileptic encephalopathies.	2017	Cohort	70	Targeted sequencing of 480 genes
12	Peng, et al.[38]	Novel West syndrome candidate genes in a Chinese cohort	2018	Cohort	72	WES
13	Zhang, et al.[39]	Pathogenic variants identified by whole-exome	2020	Cross sectional	43	WES
14	Arafat, et al.[28]	Unexplained Early Infantile Epileptic Encephalopathy in Han Chinese Children: Next-Generation Sequencing and Phenotype Enriching.	2017	Cohort	68	Targeted panel (308 genes)
15	Jiwon Lee, et al.[23]	Determining the best candidates for next-generation sequencing based gene panel for evaluation of early-onset epilepsy	2020	Cross sectional	116	Targeted gene panel on 175 genes
16	Ji-Hoon Na, et al.[26]	Targeted gene panel sequencing in early infantile onset developmental and epileptic encephalopathy	2020	Cross sectional	150	Targeted gene panel on 172 genes
17	Rikke S. Møller, et al. [40]	Gene Panel Testing in Epileptic Encephalopathies and Familial Epilepsies	2016	Cohort	216	Targeted NGS of 46 epilepsy genes
18	Krey, Ilona, et al. [41]	Genotype-phenotype correlation on 45 individuals with West syndrome	2019	Cohort	45	Sequencing panel targeting 131 genes

NGS: Next-generation sequencing; TNGS: Targeted next-generation sequencing; WES: Whole exome sequencing; WGS: Whole genome sequencing;

A total of 18 studies were included in this scoping review (Table 1). Among these, 1 study utilized whole genome sequencing (WGS), 8 applied whole exome sequencing (WES), 13 used targeted gene panels, and 2 employed a combination of WES and panel-based approaches to identify genetic causes of early-onset developmental and epileptic encephalopathies (DEE).

Summary tables of gene mutations associated with distinct DEE syndromes in infants are presented in Tables 2–5. Each table outlines typical genotype and phenotype correlations across specific syndromes, including Early Infantile DEE (Ohtahara Syndrome and Early Myoclonic Encephalopathy), West Syndrome, Dravet Syndrome, and Epilepsy of Infancy with Migrating Focal Seizures (EIMFS). These summaries highlight patterns in age of onset, seizure types, neurodevelopmental outcomes, EEG features, and treatment response.

Detailed case-level data, including individual nucleotide and protein changes, are provided in the supplementary materials (Supplementary Tables SII–SV).

Table II: Summary of Gene Mutations Reported in Early Infantile Developmental Epileptic Encephalopathy (EIDEE), including Ohtahara Syndrome and Early Myoclonic Encephalopathy (EME)

Gene	Age of Onset Types	Common Seizure Clinical	Developmental and Other Features	EEG Pattern	Imaging Findings	Medication and Outcome
Ohtahara Syndrome						
STXBP1	4 days-3 months	Spasms, TS	GDD/ID	BS, HA, MF,	Diffuse atrophy, GSW, GPFA hypomyelination, ventriculomegaly	Often resistant to AEDs
MCAT	~1 day	N/A	DD, dystonia	N/A	BA, cystic necrosis, oedema, thalamic hemorrhage	Drug-resistant
SCN8A	~3 days	TS, GTCS, Myo, FS	GDD	MF, GSW, GPFA, BS	Absent visual regard, spasticity	Partial response to DPH, VPA, CLB
ARX	~53 days	Spasms	Severe ID	BS	Normal	Initial control with ACTH & LEV; later refractory
Others						
KCNQ2 (2 cases). GNAO1, SCN2A						N/A
Early Myoclonic Encephalopathy (EME)						
SLC1A2	~2 d	Myo, TS	Profound ID	MF, slow background	Myelination of cerebellum and brain stem, thin CC, and cerebral atrophy	CBZ, LTG, LCM, pyridoxine, CZP AZD, VPA, PB, PHT, prednisolone, VGB, KD, TPM
GABRB2	~7 d	Myo, TS	Severe GDD	BS	normal	PB, LEV, MDZ, biotin, FOL, B6; intractable seizures

ACTH: Adrenocorticotropic hormone; AED: Anti-epileptic Drugs; AZD: Acetazolamide; B: Brain Atrophy; BS: Burst-suppression; CC: Corpus Callosum; CLB: Clobazam; CBZ: Carbamazepine; CZP: Clonazepam; DEE: Developmental and Epileptic Encephalopathy; DD: Developmental Delay; DPH: Phenytoin; EEG: Electroencephalogram; FOL : Folic acid; FS: Focal Seizure; GDD : Global Developmental Delay; GPFA : Generalized paroxysmal fast activity; GSW: General Sharp Wave; GTC: General Tonic Clonic Seizure; HA: Hypsarrhytmia; ID: Intellectual Disability; IS: Infantile Spasm; KD: Ketogenic Diet; LCM: Lacosamide; LEV: Levetiracetam; LTG: Lamotrigine; MDZ : Midazolam; MF: Multifocal; Myo: Myoclonic; N/A: Not Available; OS: Ohtahara Syndrome; PB: Phenobarbital; PHT: Phenytoin, TPM: Topiramate; TS: Tonic Seizure; VGB: Vigabatrin; VPA: Valproic Acid

Table III: Summary of Gene Mutations Reported in West Syndrome/Infantile Spasms

Gene	No. of Cases	Age of Onset	Common Seizure Types	Developmental and Other Clinical Features	EEG Pattern	Imaging Findings	Medication and Outcome
CDKL5	16 cases	1 day-7 month	IS, TS, GTCS, Myo	GDD, ID, movement disorder	HA, MF	Often normal, CA	Often intractable; Seizure reduction reported with ACTH
STXBP1	8 cases	1 day-9.5 months	IS, Myo, GTCS	ID, GDD	HA, GSpW	Often normal, BA	Often controlled; seizure freedom reported with VPA + TPM
KCNQ2	6 cases	1-4 days	IS, GTS	GDD, dystonia	BS, SpW	Often normal, BA, Thin CC, delayed myelination	N/A
NTRK2	3 cases	3 days-4 months	IS, FS, TS, FIA	Severe GDD, severe ID, microcephaly, hypotonia	HA, MF, DS	Optic nerve hypoplasia	Often intractable; partial response to prednisolone, ACTH, VGB
SCN2A	3 cases	5-10 months	IS, GTCS	GDD, movement disorders	BS, HA	CA	Often controlled; seizure freedom with LTG and CLB
SPTAN1	2 cases	2 weeks-5 months	IS, Myo	ID, acquired microcephaly, hypotonia	Sp, SW, HA, MF	Delayed myelination, CA, thin CC	Often resistant to AEDs
RAB11A	2 cases	4-11 months	IS, Myo, FS, FIA, GTCS	Severe GDD, severe ID, hypotonia	Modified HA	Atrophy, delayed myelination, increased subarachnoid spaces	Seizure reduction reported with LEV and LTG
Others	~20 cases	Variable	IS, TS, GTC, Myo	Variable	Variable	Variable	

ACTH: Adrenocorticotropic hormone; AED: Anti-epileptic drugs; BA: Brain atrophy; BS: Burst-suppression; CA: Cerebral Atrophy; CC: Corpus callosum; CLB: Clobazam; DS: Diffuse slowing; FIA: Focal impaired awaraness; FS: Focal seizure; GDD; Global developmental delay; GSpW: General spike and wave; GTCS: General tonic clonic seizure; GTS: General tonic seizure, HA: Hypsarrhytmia; ID: Intellectual disability; IS: Infantile spasm; LEV: Levetiracetam; LTG: Lamotrigine; MF: Multifocal; Myo: Myoclonic; N/A: Not available; sG: Secondary generalized seizure; Sp: Spike; SpW: Spike and waves; SW: Sharp waves; TPM: Topiramate; TS: Tonic seizure; VGB: Vigabatrin; VPA: Valproic acid

Table IV: Summary of Gene Mutations Reported in Dravet Syndrome

Gene	No. of Cases	Age of Onset	Common Seizure Types	Developmental and Other Clinical Features	EEG Pattern	Imaging Findings	Medication and Outcome
SCN1A	Most reported	Varied between 2 days-11 months	Febrile seizure with FT, GT, FIA, FHC, GAA, GMA, GTC, FTC, GM, FHK, Ab, H, SE, CPS, sGTC	Mild to Severe DD/ID	GSW, MF, PPR, PHR, SW	Often normal, but few BA reported	Often drug-resisant. Partial response reported with combination of OXC, VPA, TPM, CLB, ZNS, LEV, PB, KD
SCN1B	2 cases	~ 6 months	Febrile seizure with Ab, Myo, Febrile SE, GTCS	ID, Regression	Sometimes Normal; PHR SW	Normal	Partial responder to combination of VPA, LEV, CLB, ZNS, PB, and CLZ
GABRA1	4 cases	N/A	Febrile seizure with Ab, At, FDS, H, Myo, TS, GTCS, SE	Mild to Moderate ID	Sometimes normal; GSW, MF, FD, PPR	Often normal	N/A
STXBP1	3 cases	N/A	Febrile seizures with At, Ab FDS, Myo, T, TCS, SE	Often Severe ID	MF	Normal; BA	N/A
PCDH19	1 case	~ 4 months	Febrile seizure with Ab, At, FDS, FT, GT	Mild DD/ID	N/A	N/A	N/A
CHD2	1 case	N/A	Absences with head drop, fever provoked FS	Age-appropiate	Occipital, PHR SW, Eye closure sensitivity	Normal	Remission with combination of VPA, CLB, ZNS
CACN1A	1 case	N/A	Febrile seizure with GTC, Myo, CPS	ID	FSW	Normal	Resistant to AED

Ab: absence; AED: Anti-epileptic drugs; At: atonic; CLB: Clobazam; CPS : Complex partial seizure; FDS: Focal dyscognitive seizures; FHC: Focal hemiclonic; FHK: Focal hyperkinetic; FIA: Focal impaired awaraness; FSW: Fast spike wave; FT: Focal tonic; FTC: Focal tonic clonic; GAA: Generalized atypical absence; GM: Generalized myoclonic; GMA: Generalized myoclonic absence; GT: General tonic; GSW: General spike wave; GTC/GTCS: General tonic clonic seizure; H: Hemiclonic; ID: Intellectual disability; MF: Multifocal; Myo: Myoclonic; N/A: Not available; PHR: Posterior head region; PPR: Photo-paroxysmal response; SE: Status epilepticus; sGTC: Secondary generalized tonic-clonic seizure; SW: Sharp waves; TS: Tonic seizure; TCS: Tonic clonic seizures; VPA: Valproic acid; ZNS: Zonisamide

Table V: Summary of Gene Mutations Reported in Epilepsy of Infancy with Migrating Focal Seizures (EIMFS)

Gene	No. of Cases	Age of Onset	Common Seizure Types	Developmental and Other Clinical Features	EEG Pattern	Imaging Findings	Medication and Outcome
KCNT1	5 cases	1 day-1 year	FS, TS, Myo, GTCS, CPS	ID	MF, GSW, BS	Often normal; BA	Partial responder to VPA, LEV, TPM
CACNA1A	2 cases	4–5 weeks	FS, TS, GTCS	Severe ID	Migration, MF, GPFA, BA	Normal or delayed myelination	Not responder to LEV, STP, CBZ, VPA, TPM, RFM
SCN2A	2 cases	2–3 days	CPS, GTC	ID	MF	TL atrophy, BA	Controlled to AED
CLCN4	1 case	1 month	CPS	ID	MF	N/A	Remitted to AED
KCNQ2	1 case	2 days	CPS, SPS, GTCS	ID	MF	N/A	Controlled to AED

AED: Anti-epileptic Drugs; B: Brain Atrophy; BS: Burst-suppression; CBZ: Carbamazepine; CPS: Complex partial seizure; EEG: Electroencephalogram; FS: Focal Seizure; GPFA: Generalized paroxysmal fast activity; GSW: General Sharp Wave; GTCS: General Tonic Clonic Seizure; ID: Intellectual Disability; LEV: Levetiracetam; MF: Multifocal; Myo: Myoclonic; N/A: Not Available; RFM : Rufinamide; SPS: Simple partial seizure; STP: Stiripentol; TL: Temporal lobe; TPM: Topiramate; TS: Tonic Seizure; VPA: Valproic Acid

Early Infantile Developmental Epileptic Encephalopathy (EIDEE)

Ohtahara syndrome (OS)

Based on the included studies, Ohtahara syndrome was associated with a range of genetic variants, most frequently involving STXBP1 and KCNQ2, followed by MCAT, SCN8A, ARX, GNAO1, and SCN2A (Table II). Reported protein changes included p.Ala294Val, p.Ala306Val, p.Tyr231Cys, p.Arg856Gln, p.Pro480Leu, and p.Ile240Leu, while nucleotide changes were noted at c.592G>A, c.692A>G, c.2567G>A, c.881C>T, c.917C>T, c.1439C>T, and c.718A>C (see Supplementary Table SII). Most variants were de novo, and the age of seizure onset was typically within the first week of life, with a male predominance. Clinical manifestations included tonic and spasm seizures, with burst suppression as the most common EEG pattern. Treatment responses were generally poor, especially in STXBP1, MCAT, and ARX.

Early Myoclonic Encephalopathy (EME)

In EME cases, genetic variants were reported in SLC1A2 and GABRB2 (Table II), with nucleotide and protein changes including c.851C>A and p.Thr284Lys (see Supplementary Table SII). Seizure onset occurred at or before one week of age, and sex distribution was equal. Seizure types were predominantly myoclonic, followed by tonic seizures. EEG

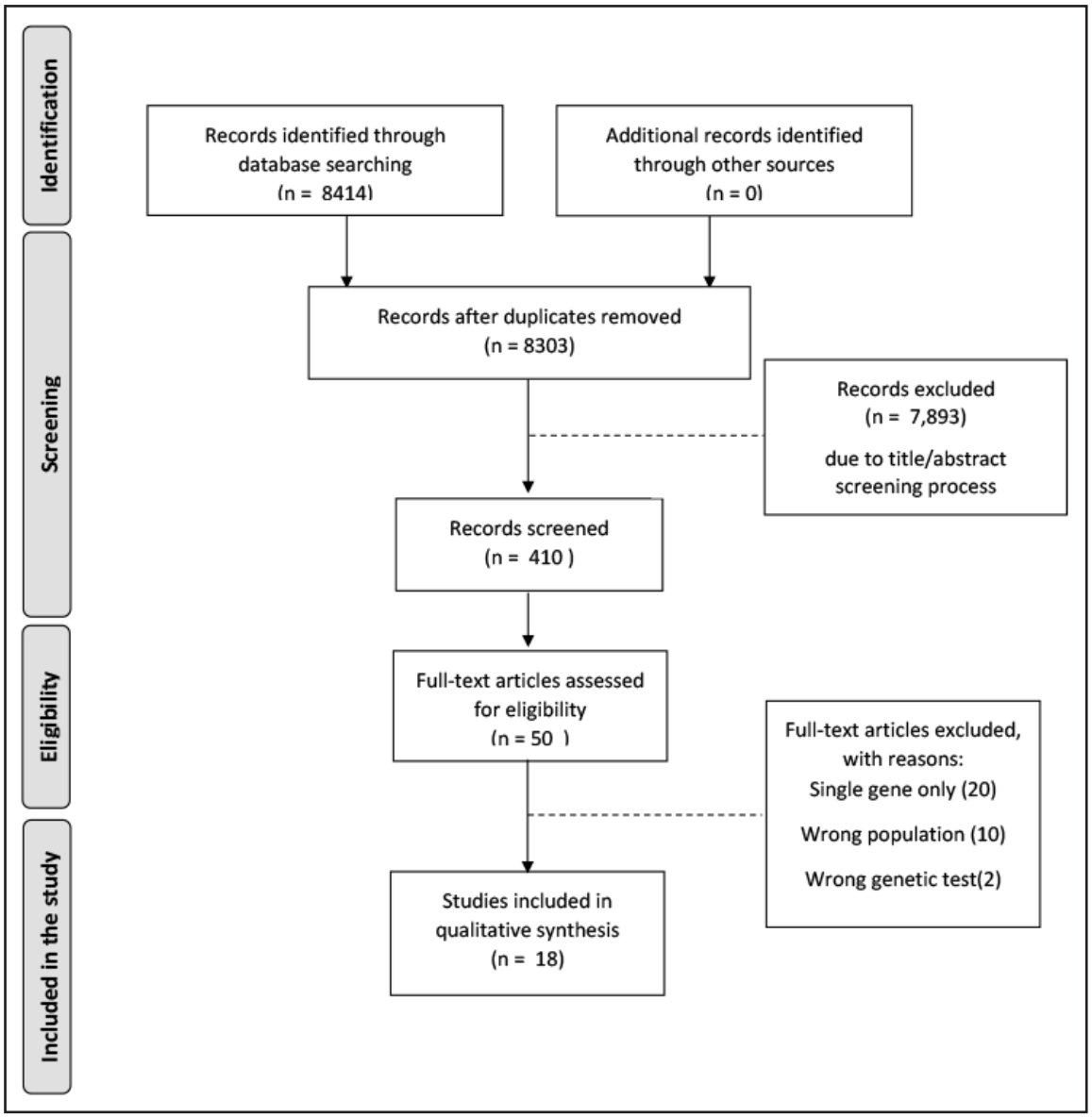

Fig. 1: Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing systematic literature search and screening

findings showed multifocal discharges, slow background activity, and burst suppression. No family testing results were reported in the included studies.

West syndrome (WS)

The most frequently implicated gene in WS or infantile spasm was CDKL5, followed by STXBP1 and KCNQ2, with various nucleotide and protein alterations (Table III). Most reported variants were de novo. Age of seizure onset ranged from 1 day to 11 months, with a female predominance. The most common seizure types were myoclonic and tonic seizures, and EEG frequently showed multifocal discharges, slow background, and burst suppression.

Treatment responses varied: while some patients remained pharmacoresistant, others showed partial improvement with Adrenocorticotropic hormone (ACTH), vigabatrin, prednisolone, valproic acid (VPA), topiramate (TPM), levetiracetam (LEV), lamotrigine (LTG), or clobazam (CLB) (see Supplementary Table SIII)

Dravet syndrome (DS)

In Dravet Syndrome, genetic variants were found primarily in SCN1A, with diverse nucleotide and protein changes. Additional gene variants identified included SCN1B, GABRA1, STXBP1, PCDH19, CHD2, and CACNA1A (Table IV). Most mutations were reported as de novo based on family testing. The age of seizure onset ranged from 2 to 8 months, with no notable difference between male and female patients. Clinically, febrile seizures were the predominant seizure type. Most patients exhibited severe developmental delay or intellectual disability. EEG findings were variable, and head imaging was typically normal. Regarding seizure outcomes, the majority of patients experienced poor seizure control (see Supplementary Table SIV).

Epilepsy of infancy with migrating focal seizures (EIMFS)
EIMFS cases involved variants primarily in KCNT1 and CACNA1A, with additional reports involving SCN2A, CLCN4, and KCNQ2. Nucleotide changes included c.1038C>G, c.2800G>A, c.1421G>A, and c.4877G>T, resulting in protein changes such as p.Phe346Leu, p.Ala934Thr, p.Arg474His, and p.Arg1626Leu (Table V; see Supplementary Table SV).

Age of onset ranged from 1 day to 1 year, with a higher occurrence in male patients. The most common seizure types were complex partial and generalized tonic-clonic seizures. EEGs often showed multifocal discharges, and brain imaging findings ranged from normal to cerebral atrophy. Most cases showed poor treatment response and severe neurodevelopmental impairment.

DISCUSSION

Developmental and epileptic encephalopathies (DEE) are progressive disorders characterized by recurrent clinical seizures that contribute to severe developmental delay, regression, and various comorbidities. In 2017, the International League Against Epilepsy (ILAE) proposed a refined classification of DEE, recognizing three overlapping categories: developmental encephalopathy, epileptic encephalopathy, and DEE, where both processes contribute to clinical deterioration.[8–10] The concept of DEE is that in infants presenting with severe early-onset epilepsy, neurodevelopmental comorbidity may be attributable to both the underlying cause and the adverse effects of uncontrolled epileptic activity.[2,8] It appears that if most genes show phenotypic heterogeneity and the most syndromes reveal genetic heterogeneity, the interpretation of this heterogeneity and its significance should be considered in the context of electroclinical presentation.[11]

This scoping review aimed to summarize the gene variants associated with infantile DEE and highlight their electroclinical correlations. In line with prior studies, gene discovery in DEE continues to reveal phenotypic overlap across multiple genes.

Early infantile developmental and epileptic encephalopathy (EIDEE) includes neonates and infants previously classified as having OS and EME. Causative pathogenic gene mutations are commonly found in a majority of patients with EIDEE.[2]

OS was linked to a variety of genetic etiologies, with STXBP1 being the most frequently reported, followed by MCAT, GNAO1, SCN2A, SCN8A, and ARX. The most common seizure types were tonic and spasm seizures, and EEGs often demonstrated burst suppression. STXBP1 is a pathogenic variant noted in 30% of patients with OS.[12] STXBP1 (more commonly known as MUNC18-1) is encoded by the STXBP1 gene (NM_003165.3), which comprises 20 exons and is located on chromosome 9q34.11.[13] The STXBP1 gene encodes the protein known as syntaxin-binding protein, SEC1/Munc18-1.[14] It refers to the SEC1 family of membrane-transport proteins, influence the presynaptic vesicular fusion process by docking and fusing with the synaptic vesicle,[15] and with the haplosufficiency of STXBP1 can lead to synaptic vesicle release impairment.[16] The current hypothesis proposes that the STXBP1-E phenotype is caused by loss-of-function mutations in STXBP1, which disrupt synaptic vesicular transport and the secretion of neurotransmitters that closely interact with SNARE proteins.[17] In our study, the protein alterations (e.g., p.Ala294Val, p.Ala306Val, p.Tyr231Cys) differed from previously reported common variants such as p.Arg406His, which has been widely associated with STXBP1-related epilepsy. A study by Xian et al. grouped 139 individuals (including 49 with OS) into six electroclinical phenotypes and found an association between burst-suppression patterns and p.Arg406Cys/His variants (OR 2.55; 95% CI 1.13–5.46). Similarly, Parrini et al. reported STXBP1 mutations including p.Arg406Cys in neonatal-onset epilepsy using a 30-gene sequencing panel.[13,14]

In EME, genetic variants were detected in SLC1A2 and GABRB2. SLC1A2, located on chromosome 11p13,[18] a key regulator of extracellular glutamate levels. Mutations in this gene lead to impaired glutamate uptake, resulting in excitotoxicity.3 Clinical manifestations in our study included myoclonic and tonic seizures, profound developmental delay, and EEG patterns with multifocal discharges and burst suppression. Previous reports described a heterozygous missense variant (c.163A>T) in SLC1A2 associated with generalized epileptiform activity and seizure onset at 40 days of life. Other studies note that SLC1A2-related epilepsy often begins with myoclonic or tonic seizures and progresses to multiple seizure types, accompanied by global developmental delay, optic nerve atrophy, and cortical visual impairment.

In the case of GABRB2, we observed a variant (c.851C>A; p.Thr284Lys) associated with myoclonic and tonic seizures, severe global developmental delay, and burst suppression on EEG. Previous reports describe different GABRB2 mutations, such as c.859A>C (p.Thr287Pro) in EME. The GABRB2 gene encodes a subunit of the GABA-A receptor, a known target of barbiturates, benzodiazepines, and ethanol.

In West Syndrome, the most commonly reported genes were CDKL5, KCNQ2, and STXBP1, with frequent de novo mutations. CDKL5 encodes a kinase involved in neuronal maturation and gene expression regulation.[19] In our dataset, seizure onset ranged from 27 days to 5 months, with a female predominance.

The most frequent seizure types were myoclonic and tonic seizures, and EEG patterns commonly showed multifocal discharges and burst suppression. The majority of patients had refractory seizures despite treatment, underscoring the need for early diagnosis and tailored therapeutic approaches. This review identified SCN1A as the primary gene associated with Dravet Syndrome (DS). SCN1A, located on chromosome 2q24.3, encodes the Nav1.1 sodium channel, predominantly expressed in inhibitory interneurons.[20] Loss-of-function mutations lead to neuronal hyperexcitability and epileptogenesis. Most SCN1A mutations were reported as de novo and were consistent with haploinsufficiency as the primary disease mechanism.[21] In our review, seizure onset on DS occurred between 2 and 8 months, aligning with known DS onset patterns.[2,22] Clinical manifestations were dominated by febrile seizures, followed by developmental regression and

intellectual disability. EEG findings were variable, and neuroimaging was often normal. Most patients experienced pharmacoresistant seizures.

EIMFS cases in our review primarily involved KCNT1 and CACNA1A, with additional variants in SCN2A, CLCN4, and KCNQ2. KCNT1 is the major gene and is reported in approximately half of patients of EIMFS.[2,23] The KCNT1 gene, which encodes the sodium-activated potassium channel, is the primary gene and is noted in approximately 50% of patients with EIMFS.[2] KCNT1, which encodes a sodium-activated potassium channel, is the most frequently implicated gene in EIMFS. Reported mutations often cluster in the C-terminal region, although some were identified in the pore and transmembrane domains. In our included studies, most patients had seizure onset between 1 and 3 months, often with tonic seizures featuring focal elements. EEG findings were diverse but typically showed multifocal activity, and imaging was often normal or showed brain atrophy. Most patients experienced severe developmental delay and poor seizure control.

In reviewing the genotype and phenotype correlations, several patterns emerged across syndromes. For example, KCNQ2 variants, frequently reported in Ohtahara Syndrome and West Syndrome, were commonly associated with early neonatal onset and burst suppression patterns on EEG, consistent with more severe DEE presentations.[24–26] Similarly, STXBP1 variants, also linked to both Ohtahara and West Syndrome, were associated with intractable seizures, global developmental delay, and characteristic EEG abnormalities, such as burst suppression in Ohtahara and hypsarrhythmia in West Syndrome.[25–29] In cases of EIMFS, KCNT1 mutations were consistently correlated with multifocal EEG discharges, very early onset, and poor response to antiepileptic treatments, reinforcing its role in more severe phenotypes.[26,27,30] Although genotype and phenotype associations were heterogeneous, these patterns suggest that certain gene variants may be predictive of specific electroclinical features and disease severity in DEE.

Genetics has made significant advancements, which have benefited our capacity to diagnose DEE in the context of clinical practice.[31] Genetic variants may be noted in patients with early onset epilepsy at a high frequency as it is highly suspected to have a genetic origin.[26] A high proportion of infants with early-onset epilepsy have an underlying genetic cause, and early identification via NGS (WES, WGS, or targeted panels) can shorten the diagnostic journey. In addition to confirming diagnosis, genetic insights support prognosis estimation, treatment planning, and even clinical trial eligibility. It can contribute to the prediction of disease progression and assist in making informed decisions regarding treatment options.[31]

STRENGTHS AND LIMITATIONS OF THE STUDY

This is the first scoping review to describe genetic factors involved in DEE in infants. All studies included in this review were assessed as being of high quality. However, the limitations of this study included the absence of information on the participants. To conduct a more comprehensive systematic review and even meta-analysis, more observational research on genetic mutations in DEE is required.

CONCLUSION

This review identified several key genetic variants, including STXBP1, SLC1A2, CDKL5, SCN1A, and KCNT1, which are commonly found in infants with developmental and epileptic encephalopathies (DEEs), each associated with different clinical features and implications. Our findings reinforce the growing role of next-generation sequencing (NGS) in supporting early and accurate diagnosis, which can help guide more personalized treatment decisions. By summarizing current genetic patterns in infantile-onset DEE, this review contributes to a clearer understanding of the genetic landscape and highlights the value of incorporating genetic testing into routine clinical care. Future studies should focus on evaluating how early genetic diagnosis influences long-term outcomes and how genetic findings can be translated into targeted therapies, especially in resource-limited settings.

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AT, ESH, and G made substantial contributions to the conception and design of the work. AT, KHM, and KI contributed to data acquisition. AT, ESH, KI, and G performed the data analyses and the interpretation of the data. AT, ESH, and KHM drafted the text and prepared the figures. AT, ESH, KHM, KI, and G read and approved the final manuscript. All authors approved the present version for publication and are accountable for all aspects related to the study.

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