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Developmental and Epileptic Encephalopathies

Aetiology, clinical presentation, and comprehensive genetic testing for personalised targeted therapy

Developmental and epileptic encephalopathies (DEEs) are a heterogeneous group of neurological disorders with developmental impairment due to both the underlying cause and exacerbation by frequent seizures and epileptiform abnormalities on EEG[1]

Aetiology[1]

Genetic

- Specific gene defects cause recognisable syndromes
- Multiple genetic variants may be associated with the same epilepsy syndrome

Non-genetic

Structural, metabolic, infectious, or immune factors

Combination of genetic and environmental factors

Epilepsy[1]

Uncontrolled, frequent, or prolonged seizures

Developmental abnormalities[1]

- Autism spectrum disorder
- Behavioural disorders
- Psychosis
- Depression

- Developmental impairment precedes seizure onset in some patients[2]
- Cognitive deterioration may progress even after complete seizure control[2]

Symptoms for the diagnosis of DEE[3,4]

Frequent drug-resistant seizures	Epileptiform activity on the EEG	Developmental slowing or regression

• Seizure types
  ◦ Epileptic spasms
  ◦ Tonic, atonic, focal, and generalised seizures
  ◦ Atypical absences[1]
	• Abundant diffuse or multifocal epileptiform discharges
	• Diffuse slowing of the background on EEG
	• Distinct patterns
	  ◦ Hypsarrhythmia
	  ◦ Burst-suppression
	  ◦ Periods of attenuation and slow spike-waves
		• Cognitive and motor function decline
		• Neurodevelopmental comorbidities[3]
		  ◦ Autism spectrum disorders
		  ◦ Movement and behavioural disorders or psychosis

Underlying aetiology contributing to developmental impairment

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Diagnostic testing for DEEs in children with developmental delay and epilepsy[5]

- Medical history of the patient and family
- Physical examination
- Neuroimaging/ magnetic resonance imaging
- Neurodevelopmental assessment
- Genetic testing
- EEG study
- Metabolic assessment

DEEs are genetically and phenotypically heterogeneous, and accurate differential diagnosis of DEEs that is defining both epilepsy syndrome and aetiology can aid in selection of optimal treatment[2,5,6]

Optimised seizure control can minimise contribution of epileptic activity to cognitive impairment

Patients with infantile epileptic spasms syndrome → Early control of spasms to improve developmental outcomes[7]

Genetic testing identifies specific pathogenic variants in DEEs

>900 genes causative for DEEs[4]

Among DEE patients[1]:

De novo copy-number variants: 8%

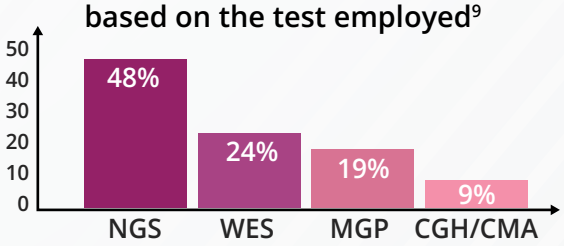
Recessive pathogenic variants: 11–38%

30–50% of DEE caused by *de novo* pathogenic variants in single genes[1,5]

Advanced genetic testing approaches[5]

- Comparative genomic hybridisation (CGH) arrays/ chromosomal microarray analysis (CMA)
- Epilepsy multi-gene panel (MGP)
- Whole exome sequencing (WES)
- Whole-genome sequencing (WGS)
- Next-generation sequencing (NGS) for indels and complex structural variants
- Karyotyping for ring chromosomes[8]

Diagnostic yield of genetic testing varies based on the test employed[9]



Guidelines for comprehensive multi-gene testing in DEE diagnostics[9]

Evidence-based clinical recommendations for unexplained DEE

Genetic testing is strongly recommended as a first-tier test for all individuals with unexplained DEE without any age limitations

- Whole exome/genome sequencing
- MGP ○ 100–299 genes[10] ○ Copy-number analysis

Exome/genome sequencing is conditionally recommended over MGP

Genetic tests should be selected, ordered, and interpreted by a qualified healthcare provider in the setting of appropriate pre-test and post-test genetic counselling

NICE guidelines[11]

• WGS for patients with DEE of unknown cause aged:	○ <2 years	○ 2–3 years (if clinically agreed by a specialist multidisciplinary team)
• WGS for individuals of any age with clinical features:	○ Genetic epilepsy syndrome	○ Additional signs, such as intellectual disability, autism, dysmorphism, congenital anomalies, or unexplained cognitive decline
• WGS for patients with early epilepsy onset:	○ <5 years	○ +/– Additional signs, such as intellectual disability, autism, dysmorphism, congenital anomalies, or unexplained cognitive decline

NICE: National Institute for Health and Care Excellence

Including genetic counsellors in neurology practices and/or referral to genetics specialists will support providers in implementing these recommendations[7]

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Benefits of integrating genetic testing[5]

Genetic testing helps identify the cause in 30–50% of DEE cases[5]

- Improves understanding of DEE pathophysiology[5]
  - Identify the impact of previously unknown variants
- Direct towards appropriate resources[6]
  - Refer to gene-specific clinical trials

- Helps with prognosis and counselling on:
  - Risk of recurrence
  - Developmental outcomes
  - Risk of sudden unexpected death in epilepsy
  - Identifies at-risk family members
  - Family/pregnancy planning and prenatal genetic testing
- Helps in the development of personalised therapies[5,9]
  - Inform antiseizure medication selection
  - Initiation of ketogenic diet
  - Alter plans for epilepsy surgery

Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD)

CDD is a DEE caused by dysfunctional kinase activity of the CDKL5 protein[2,12]

Annual global incidence of CDD[2]
1 per 40,000 to 50,000

Females are predominantly affected[12]
4:1 (female:male)

CDD is typically caused by a *de novo* pathogenic variant, with a single occurrence in a family[12]

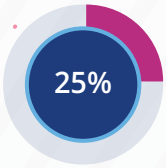
Disease severity of X-linked CDD depends on[12]:

- Type and position of the *CDKL5* pathogenic variant
- Pattern of X chromosome inactivation in females
- Presence of postzygotic mosaicism in males or females

Clinical presentation of CDD

Distinctive seizure types that vary over time[2,12]

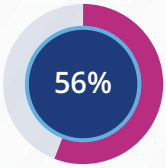
Infancy



Epileptic spasms (50% without hypsarrhythmia)

- No significant epileptiform abnormalities in EEG in early infancy but may be seen in late infancy

Later



- Multiple-phase seizures[2]
  - Hypermotor–tonic–spasm sequence
- Other seizure types: Tonic, focal, myoclonic, and generalised tonic-clonic seizures
- Long periods without seizures in the first two years or more[2]
  - Frequent and multifocal epileptiform discharges

Developmental challenges[12]

Cortico visual impairment

Tone abnormalities

Sleep disturbances

Movement abnormalities

Gastrointestinal problems

Respiratory and behavioural problems

Treatment options[12,13]

- Level 4 epilepsy center with expertise in management of DEE or a Center of Excellence is needed
- Multidisciplinary supportive care
- Annual assessments recommended

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Targeting the *CDKL5* gene for personalised treatment of CDD

CDKL5 protein is the predominant isoform in the central nervous system, and its kinase activity is critical for normal brain development[2]

CDKL5 pathogenic variants are typically loss-of-function variants

Targeted gene therapies are promising for improving outcomes in children resistant to existing treatments for DEE and who have a poor prognosis[5]

Potential of targeted therapies for improving patient outcomes

Genetic testing enables personalised therapy according to the patient's unique genetic profile[5]

Genetic epilepsies that benefit from precision therapy include[5,12]:	
KCNQ2	Carbamazepine (FDA approved[14]), phenytoin (FDA approved[15])
CDKL5	Ganaxolone (approved in the United States, European Union, United Kingdom[16] and China[17]), fenfluramine (not approved), and cannabidiol (not approved)
PCDH19	Clobazam (not specifically approved by FDA for *PCDH19*)
mTORopathies	Mammalian target of rapamycin inhibitors (everolimus[18]; approved in United States and European Union[19])
SCN1A loss-of-function variants	• Cannabidiol, fenfluramine, and stiripentol for Dravet syndrome (approved in the United States, European Union, United Kingdom[20], and Japan[21]) • Avoid sodium channel blockers that worsen seizures
KCNQ2, SCN2A, and *SCN8A* gain-of-function variants	Ion sodium channel blockers

Key messages

- **DEEs are complex conditions, and efforts should be made to reach a precise diagnosis as early as possible, permitting the identification of the most effective treatment**
- **Comprehensive early genetic testing is recommended for all individuals with unexplained epilepsy without any age limitations, appropriately supported by genetic counselling**
- **Improved understanding of the patient's unique genetic profile may enable personalised, targeted therapy and potentially pave the way for precision gene therapy**

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