Genetic testing in childhood epilepsy: what tests to send, whom to test, and why to test?

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ABSTRACT

The role of genetics in childhood epilepsy has significantly expanded with the advancements in next-generation sequencing technologies. Genetic testing now plays a crucial role in diagnosis, prognosis, and precision therapeutics, particularly in developmental and epileptic encephalopathies and drug-resistant epilepsies. However, implementation remains uneven, leaving clinicians with frequent questions: Which test should I choose? When is testing justified? And why does it matter just beyond a molecular label? This review aims to synthesize current evidence on the utility of genetic testing in epilepsy, comparing available modalities, identifying the clinical scenarios where testing has the most impact, and outlining the therapeutic implications.

Keywords : Childhood epilepsy, gene, WES, WGS

RESUME

Le rôle de la génétique dans l'épilepsie de l'enfant s'est considérablement renforcé avec l'essor des technologies de séquençage de nouvelle génération. Les tests génétiques constituent désormais un outil central pour le diagnostic, l'évaluation pronostique et la mise en place de stratégies thérapeutiques de précision, en particulier dans les encéphalopathies développementales et épileptiques ainsi que dans les épilepsies pharmaco-résistantes. Leur intégration en pratique clinique demeure toutefois hétérogène, exposant les cliniciens à des interrogations persistantes : quel test privilégier, à quel moment le prescrire et quelle valeur attribuer aux résultats au-delà d'une simple étiquette moléculaire ? Cette revue a pour objectif de synthétiser les données actuelles sur l'utilité des tests génétiques dans l'épilepsie, de comparer les différentes approches disponibles, d'identifier les contextes cliniques où leur impact est le plus déterminant et de préciser leurs implications thérapeutiques.

Mots clés : Épilepsie de l'enfant, gène, WES, WGS.

I-INTRODUCTION

Epilepsy is one the most common neurological disorders globally, affecting an estimated 60 million individuals. It is more prevalent in children, with a rate of 4–6 per 1,000 children, and more common in Arab populations compared to Western countries (1,2). Epilepsy is increasingly recognized as a group of heterogeneous disorders rather than a single disease entity. While clinical evaluation, electroencephalography, and neuroimaging are essential for the diagnosis and classification of epilepsy, the International League Against Epilepsy (ILAE) recognizes the growing importance of understanding the underlying causes of epilepsy. These causes can include structural anomalies, infectious factors, immune-mediated factors, genetic and metabolic factors, among others (3). The role of genetic testing in clini¬cal pediatric neurology has significantly increased in recent years, with epilepsy being no exception. This progress is largely driven by advances in molecular technologies, particularly next-generation sequencing (NGS) (4,5). The contribution of genetic discoveries has transformed the field of epilepsy, with more than 900 genes now implicated in the condition. Similar to other complex diseases, epilepsy arises not only from monogenic changes but also from the interaction between environmental and polygenic risk factors. For many pa-

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tients, especially those with early-onset or drug-resistant epilepsy, genetic testing is no longer optional but integral to clinical care (4,5). A genetic diagnosis has significant positive implications for patients and their families. It can reduce unnecessary and often invasive investigations, facilitate therapy adjustment, and enable the use of targeted anti-seizure medications for specific etiologies.

This review will address three key clinical questions: *Which tests should be ordered? Whom to test? What are the clinical benefits from testing?*

II- Which tests should be sent?

The choice of genetic test depends on the clinical context, including the specific epileptic syndrome and associated comorbidities, suspected etiology, and available resources (Table 1).

Table 1: Genetic tests in epilepsy: advantages and limitations

	Karyotype	CMA	Multigene epilepsy panel	WES	WGS
Single nucleotide variants	–	–	Coding region	Coding region	Coding and noncoding regions
Indels	–	–	+	+	+
Copy number variants		Exon, single gene, multigene	Exon, single gene	Exon, single gene, multigene	Exon, single gene, multigene
Trinucleotide repeat expansion	–	–	–	–	+
Deep intronic variants	–	–	–	–	+
Structural rearrangements	Unbalanced	Unbalanced	–	–	Balanced and unbalanced
Incidental findings	–	–	–	+	+
Candidate or novel genes	–	–	–	+	+
Faster turnaround time	+	+	+	+	++
Cost of testing	+	+	+	++	+++
Diagnostic yield	Very low	5-15%	Up to 30%	Up to 50%	Up to 65%

WES, whole-exome sequencing; WGS, whole-genome sequencing; CMA, chromosomal microarray. +: less costly; ++: more costly

With more than 900 epilepsy-related genes identified, and additional genes continuously being discovered, broad sequencing approaches are generally preferred (4,5). Whole-exome sequencing (WES) targets the protein-coding regions of the genome, which represent less than 2% of the genome but harbor the majority of known pathogenic variants. Whole-genome sequencing (WGS), by contrast, interrogates the entire genome, including noncoding regions, and provides a diagnostic yield approximately 15% higher than WES. However, barriers such as the complexity of interpreting noncoding variants, high data storage demands, and cost continue to limit its widespread clinical adoption. It is important to highlight that WES platforms differ in their design and coverage. Extended exome sequencing approaches, which include deep intronic and regulatory regions, have been reported to achieve diagnostic yields approaching those of WGS (6). Current guidelines recommend WES or WGS as first-line tests in children with epilepsy (7,8). Targeted gene panels remain in use, but their utility is limited by variability across laboratories. Therefore, ILAE guidelines suggest using panels only when WES or WGS is not accessible (8). Comparative genomic hybridization (CGH) arrays can detect pathogenic copy number variants (CNVs) in 5–16% of children with epilepsy, particularly in those with neurodevelopmental comorbidities. Some genetic causes of epilepsy remain difficult to detect: repeat expansions (e.g., FMR1-related fragile X syndrome, CSTB-related Unverricht-Lundborg progressive myoclonic epilepsy), noncoding variants, ring chromosomes (detected by karyotype), and methylation defects such as UBE3A in Angelman syndrome. While testing primarily addresses monogenic epilepsies, many familial cases are polygenic; testing individuals for polygenic risk of epilepsy is currently not avail¬able in clinical practice (7,8).

III- Whom to test?

Recommendations for genetic testing in epilepsy differ across different international guidelines. According to the evidence-based practice guidelines by the National Society of Genetic Counselors and American Epilepsy Society (7), genetic testing is strongly recommended for any unexplained epilepsy, irrespective of age. Similarly, the Genetics Commission of the ILAE Task Force (8) highlights the importance of incorporating genetic testing into clinical practice, particularly when the probability of identifying an underlying etiology is high (Table 2).

Table 2: Common indications for genetic testing in children with epilepsy

Indication	Examples
Drug-resistant epilepsy, especially of unknown cause	Defined as the inability to control seizures even after two adequate treatment attempts with well-chosen and tolerated medications, either alone or in combination
Epilepsy plus	Neurodevelopmental disorders Autism spectrum disorders Dysmorphic features Multiple congenital anomalies Extraneurologic features Movement disorders
Developmental and epileptic encephalopathies (DEE)	- Early infantile DEE (Ohtahara syndrome and early myoclonic encephalopathy) - Epilepsy of infancy with migrating focal seizures - Infantile epileptic spasms - Dravet syndrome - Epilepsy with myoclonic atonic seizures - Lennox-Gastaut syndrome - Developmental and epileptic encephalopathy with spike-and-wave activation in sleep and epileptic encephalopathy with spike-and-wave activation in sleep.
Others	-Genetic epilepsy with febrile seizures -Progressive myoclonic epilepsy -Autosomal dominant sleep-related hypermotor epilepsy -Neurodegeneration -Metabolic disorders -Malformations of cortical development -Family history of epilepsy in two first-degree family members

Genetic testing in children with epilepsy is commonly recommended in cases of drug-resistant epilepsy of unknown cause. It is also warranted in epilepsy plus presentations, where seizures coexist with neurodevelopmental disorders, autism spectrum disorders, dysmorphic features, multiple congenital anomalies, as well as cases with extraneurologic manifestations. Another major indication is developmental and epileptic encephalopathies (DEE), which include early infantile syndromes such as Ohtahara syndrome and early myoclonic encephalopathy, epilepsy of infancy with migrating focal seizures, infantile epileptic spasms, Dravet syndrome, epilepsy with myoclonic atonic seizures, Lennox-Gastaut syndrome, and syndromes with spike-and-wave activation in sleep. Finally familial epilepsies, including genetic epilepsy with febrile seizures, progressive myoclonic epilepsy, and autosomal dominant sleep-related hypermotor epilepsy, represent additional strong indications for genetic evaluation.

The criteria outlined here represent the most frequent indica¬tions for genetic testing in pediatric epilepsy, though they are not exhaustive. Certain genetic epilepsies present with distinctive phenotypic features that clinicians should recognize. Notable examples include tuberous sclerosis complex, progressive myoclonic epilepsies, and neuronal migration disorders.

IV- Diagnostic yield

The diagnostic yield of genetic testing in pediatric epilepsy varies widely, typically ranging from 20 to 65%, depending on the inclusion criteria and test used (Table 1). The diagnostic yield is higher for whole-exome sequencing (WES), reaching over 60% in some cohorts (4,9,10). Factors influencing yield include the specific epilepsy syndrome, the presence of intellectual disability or other neurodevelopmental comorbidities, and the chosen sequencing technology (WES generally offering higher yields than panels or chromosomal microarray). Another important point highlighted by several studies is the significant role of epilepsy types and syndromes in determining the diagnostic rate of the test used. In this study, we showed that in Arab populations compared to Western populations: we have a higher diagnostic rate (60 % compared to 40%), and most of the identified genes are recessive compared to dominant inheritance (10).

V- Why to Test-Clinical effects?

Beyond establishing etiology, genetic testing increasingly guides clinical management by informing treatment selection (Tables 3 and 4), refining prognosis, and supporting genetic counseling (11-13).

Table 3: Common treatable inherited metabolic epilepsies

Gene	Epilepsy syndrome	Suggested precision medicine
ALDH7A1	Vitamin B6-deficient epilepsy	Pyridoxine, lysine-restricted diet
PNPO	Vitamin B6 – deficient epilepsy	Pyridoxal-5-phosphate
PLPBP	Vitamin B6 – deficient epilepsy	Pyridoxine, pyridoxal-5-phosphate
CAD	Developmental and epileptic encephalopathy	Uridine
Folate cycle genes: *FOLR-1, MTHFR, DHFR, PCFT*	Cerebral folate transporter deficiency (ataxia and refractory myoclonic epilepsy)	Folinic acid, 5-methyltetrahydrofolate
PIGA	X-linked recessive multiple congenital anomalies – hypotonia – seizures syndrome (MCAHS2), epileptic encephalopathy	Ketogenic diet
***SLC2A1* (GLUT1)**	GLUT1 deficiency syndrome	Ketogenic diet
BTD	Biotinidase deficiency	Biotin
HLCS	Holocarboxylase synthetase deficiency	Biotin, high dose
TPP1	Neuroral ceroid lipofuscinoses type 2	Enzyme replacement therapy

In the study by Yong Koh et al., genetic testing in childhood epilepsy showed significant clinical impact. Among those who received a confirmed genetic diagnosis and were followed over time, 41% of patients experienced documented changes in management or outcomes directly attributable to their genetic findings (11). Specific variants predict therapeutic response or contraindications. For example, SCN1A variants the use of sodium channel blockers (i.e., lamotrigine), while TSC1/TSC2 variants identify candidates for mTOR inhibitors, ALDH7A1 variants supports the use of pyridoxin and lysine restricted died, and SLC2A1 variants support the use of ketogenic diet therapy. These insights prevent harmful interventions and enable precision therapy. Genetic results also refine expectations for disease progression, comorbidities, and long-term outcomes, while providing essential information for family counseling. At the healthcare systems level, molecular diagnosis shortens the "diagnostic odyssey," reduces unnecessary investigations, and opens access to gene-targeted clinical trials and experimental therapies. This linking patient care with translational research (11-13).

Table 4: Current precision medicine in genetic epilepsies

Gene	Epilepsy syndrome	Suggested precision medicine
SCN1A	Dravet syndrome	- Avoid sodium channel blockers - Stiripentol - Fenfluramine - Cannabidiol - Antisense oligonucleotide
SCN2A	Ohtahara syndrome, early encephalopathy	Sodium channel blockers
SCN3A	DEE	Sodium channel blocker
SCN8A	DEE	- Sodium channel blockers - Antisense oligonucleotide
KCNA2	DEE	4-aminopyridine
KCNQ2	DEE	Sodium channel blockers, retigabine, gabapentin
KCNT1	Epilepsy of infancy with migrating focal seizures, nocturnal frontal lobe epilepsy	- Quinidine - Antisense oligonucleotide
PRRT2	Benign familial infantile epilepsy, paroxysmal kinesigenic dyskinesia	Sodium channel blocker
GRIN2A	EE-CSWS Epilepsy-aphasia	Memantine
GRIN2B	DEE	Radiprodil Memantine
TSC1, TSC2	West syndrome Focal onset seizure	mTOR inhibitors (Rapamycin, Everolimus)
DEPDC5	Focal onset seizure	mTOR inhibitors

DEE: developmental and epileptic encephalopathy
EE-CSWS: epileptic encephalopathy with continuous spike and wave in sleep

VI- Limitations of genetic testing

Despite its benefits, the implementation of genetic testing in epilepsy remains inconsistent worldwide. In many health systems, testing is not a standard part of care, and the available techniques may be limited in scope, which reduces the diagnostic yield. Interpretation challenges, particularly the high frequency of variants of uncertain significance, further complicate clinical use. Economic barriers are also significant: in cases where testing is not reimbursed, costs often fall on families, limiting accessibility and creating disparities. Access is further constrained by shortages of specialized genetic counseling services and unequal distribution of genomic resources across regions.

VII- Conclusion

Genetic testing is no longer ancillary in epilepsy care; it is a decisive tool that can guide therapy, define prognosis, and inform families. The integration of genetic testing into childhood epilepsy practice marks a shift toward precision neurology. Evidence supports early testing in severe pediatric epilepsies as first-line, with increasing adoption of exome and genome sequencing over restricted panels.
In the Maghreb and the wider MENA region, adoption of genetic testing remains limited due to high costs, inadequate infrastructure, dependence on overseas laboratories, and a shortage of trained geneticists and counselors. Limited reimbursement and high rates of consanguinity contribute to the regional burden of recessive epilepsies, emphasizing the importance of accessible testing. To address these challenges, investment in local sequencing, regional databases, clinician training, and supportive policies is necessary. Tailored strategies are essential to ensure the benefits of precision medicine in epilepsy reach patients across the region.
Future directions include:
- More widespread use of WGS as costs decrease.
- Integration of polygenic risk scores for common types of epilepsy.
- Utilization of multi-omics (genomics, transcriptomics, metabolomics) to better understand complex pathophysiology of the condition.
- Expansion of gene-target therapies and antisense oligonucleotide approaches.

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