3

Epilepsy Genetics: Advancements in the Field and Impact on Clinical Practice

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Abstract: During the first decade of the 21st century, the landscape of epilepsy genetics started to take shape with the discovery of many new genes linked to epilepsy. These genetic discoveries advanced our understanding of the molecular and cellular pathways involved in epilepsy. Over the following ten years, the availability of clinical genetic testing along with rapidly growing knowledge of epilepsy genetics transformed patient care; most profoundly affecting management of childhood-onset epilepsies. This new genomic era offers great opportunities for the advancement of health outcomes and epilepsy research. It has also created new demands and challenges for physicians practicing in this rapidly evolving field, which requires specialized expertise in order to provide best care for patients

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and their families. This chapter reviews epilepsy genetics advancements and its impact on clinical practice.

Keywords: childhood epilepsy; clinical impact; epidemiology of epilepsy; epilepsy genes; genetics of epilepsy

INTRODUCTION

Advancements in epilepsy genetics over the past 20 years have revolutionized the diagnosis and management of epilepsy, as well as some basic concepts of our understanding. This progress may have had the greatest impact on individuals with childhood-onset epilepsy. In this chapter, we provide an overview of the current knowledge of epilepsy genetics and its impact on clinical practice. We describe the epidemiology of genetic epilepsies, review the progress made in scientific methods and technology which allowed for the current widespread use of genetic testing in clinical practice, and provide a brief report of some upcoming methods and genetic tools currently used in research and likely to come to the clinical domain in the coming years. We then describe how genetic insights have transformed some of the basic concepts of epilepsy in children and examine the implications and impact of molecular diagnosis on patient care. Lastly, we review recommendations regarding metabolic and genetic evaluation of early onset epilepsy, discuss some of the complexities and challenges that clinicians face in the evaluation and interpretation of genetic tests, and suggest a clinical practice model to best apply the expanding scientific knowledge of epilepsy genetics in clinical practice.

OVERVIEW

Historically, over 75% of all epilepsies were described as idiopathic, only in 25% or less a specific cause was known, such as congenital lesion, neoplasm, birth anoxia, infection, trauma, or stroke. Subsequently, hereditability studies revealed a role for genetic factors in epilepsies (1). With the genomic era and advances in genetic technology, the genetic etiology of several epilepsies became clear (2–7). Genomic sequencing technologies facilitated the discovery of over 100 genes involved in epilepsy and an expanding number of genetic causes have been recognized in epilepsies that were previously considered to be idiopathic epilepsies (2, 3, 5). Additionally, epilepsies previously thought to solely be caused by acquired conditions—such as perinatal stroke, infection, inborn errors of metabolism, and structural/cortical malformations—are now known to have genetic contributions (8).

Genetic epilepsies comprise a group of clinically heterogenous disorders. These disorders can be further sub-grouped into specific epilepsy syndromes based on age of onset, seizure type, EEG background, associated clinical phenotypes (including severity of developmental delay and presence of dysmorphic features) (9). For example, gene mutations may selectively cause epilepsy

(e.g., *SCN1A* mutations cause epilepsies with febrile seizures plus), may be associated with epileptic encephalopathies (e.g., *SCN1A* variants are also responsible for 70–80% of cases of Dravet syndrome), or may be causative of brain malformations and epilepsy (e.g., mutations in *TSC1* and *TSC2* genes cause tuberous sclerosis). Individually, each disorder classified as a genetic epilepsy is rare. Yet providing a molecular diagnosis may have important implications as many genetic epilepsies are potentially treatable. Thus, identifying the underlying genetic disorder can help direct pharmacotherapy, specialized diets, or surgery.

It should be noted that the associated phenotype of a genetic variant may differ for the same gene. For example, as discussed above, mutations in *SCN1A* are responsible for 70–80% of the cases of the developmental epileptic encephalopathy, Dravet syndrome. In contrast, *SCN1A* variants are also associated with the milder phenotype genetic epilepsy with febrile seizures plus. Although genes may be known to be associated with epilepsies, their specific pathogenic role and the associated phenotype may differ according to multiple factors including the precise gene mutation. Furthermore, different genes from non-overlapping pathways may result in common phenotypes. For instance, *SCN1B*, *GABRG2*, *HCN1* and *SCN8A* are reported to be associated with the Dravet syndrome. A specific genetic epilepsy or epileptic syndrome may have several different genetic causes.

The genetic variations seen in genetic epilepsies are also heterogeneous. The changes in the human genome that contribute to epilepsy vary and include monogenic variants such as *SCN1A* and *KCNQ2*-related epilepsies. Copy number variants and other structural variants, such as 15q11-q13 duplication syndrome (10, 11), have also been identified as genetic rearrangements that impact genes affecting epilepsies. Additionally, polygenic and complex variants as well as epigenetic mechanisms have a reported role in genetic epilepsies (12, 13). Despite recent rapid progress during the genomic era, there is much to be learned about the role of epigenetics, structural variants, and multigenic causality in human epilepsy and there is an ongoing need for continued discovery of novel pathogenic genes in genetic epilepsies (14, 15).

EPIDEMIOLOGY

The estimated lifetime prevalence of epilepsy is 7.60 per 1000 individuals (16) and approximately 50–65 million individuals are affected worldwide (16, 17). Epilepsy has a bimodal age distribution, with the highest incidences (>60 per 100,000) found in those less than 5 years and over age 65 years of age (18, 19). In the United States, over 470,000 children have epilepsy (19). In a recent multicenter study of pediatric epilepsies in Scotland, the overall estimated annual incidence of single-gene epilepsies was 1 per 2120 live births (47.2/100,000) (7). The adjusted incidence of childhood-onset epilepsies in children under 3 years of age in Scotland was 239 per 100,000 live births (20). The proportions of monogenic, polygenic, and complex epilepsies remain unknown.

In children, the age of onset of seizures or developmental delay onset significantly correlates with the genetic etiology. Children with onset of epilepsy before 3 years of age are more likely to have a higher burden of cognitive and neuropsychological comorbidities. Additionally, this younger symptom onset is associated

with a higher seizure burden and a greater risk for having a developmental epileptic encephalopathy (9, 21). The death rate in developmental epileptic encephalopathies is markedly elevated (743 per 100,000 person-years) due to poorly-controlled seizures as well as non-neurological comorbidities including respiratory insufficiency (22). In contrast, the death rate in children with uncomplicated epilepsy mirrors the general pediatric public (36 per 100,000 person-years) (22). There is a significant role for molecular testing in the diagnosis of genetic epilepsies. Molecular testing leads to identification of causative mutations in approximately 30% of children with genetic epilepsies and up to 50% in children with developmental and epileptic encephalopathies, which frequently have a genetic etiology and often arise *de novo* (2-6, 23, 24). Early identification of underlying genetic diagnoses in developmental epileptic encephalopathies may allow for prognosis determination, treatment and management optimization, seizure reduction and potential improvement in developmental outcomes.

Large-scale sequencing studies have significantly contributed to our understanding of rare monogenic variants in epilepsy. The Epi4K Consortium analyzed the genomes of 525 individuals with familial focal epilepsy and 640 individuals with familial genetic generalized epilepsy (25). The study revealed an enrichment of pathogenic variants within 43 known epilepsy genes, many of which had only been associated with epileptic encephalopathies, in individuals with epilepsy which were absent in the 3877 controls (25). In the EuroEPINOMICS consortium, an enrichment of 19 variants of the gene encoding GABA-A receptor subunits were found in 1092 individuals (three cohorts) with genetic generalized epilepsy but not in 2669 controls (26). The ongoing Epi25 collaborative has completed analysis of 9,170 epilepsy-affected individuals and 8,436 controls and the work continues to show a clear role of genetics across both rare and common forms epilepsy (4).

METHODS AND TECHNOLOGY PROGRESS – FROM BENCH TO BEDSIDE

Technological advancements made possible by the completion of the Human Genome Project in 2003 have been the driving force accelerating recent gene discovery in epilepsy. Genome-wide comparative array hybridization and genome-wide genotyping approaches that use small complementary DNA probes targeting genomic loci or polymorphisms across the genome allowed for the first possible genome-wide scans for copy number variants. This technological advancement led to the identification of multiple recurrent microdeletions that increased the risk of epilepsy, including 15q13.3, 15q11.2, and 16p13.11 (27–29), and provided the first early support for an important role for rare, highly penetrant *de novo* variants in epilepsy. Next-generation sequencing was the next major technological advancement that further enlightened the community to the role of rare highly penetrant genetic variants in severe sporadic subtypes of epilepsy. This technology that performs massively parallel sequencing of amplified genomic fragments allowed for the first systematic sequencing of all the protein coding regions of the genome. This technology readily led to the identification of thousands of pathogenic genetic variants in more than a hundred novel epilepsy genes and continues to lead to novel gene discovery more than ten years since the technology became available. Many of the newly discovered pathogenic variants were

found to be newly acquired in the genomes of individuals with developmental and epileptic encephalopathies which has shaped the current understanding of the genetic architecture of epilepsy. It should be noted that the value of these technological advancements was not only in how they illuminated pathogenic variants in patients but also in how they allowed for the characterization of the landscape of genetic variants in the general population, essentially establishing the baseline for which patient genomes could be compared (30, 31). While genome-wide association studies looking for associations of common haplotypes with epilepsy risk did not lead to the identification of genetic variants of large effect sizes in epilepsy (32), there is increasing appreciation that combinations of genetic variants across the allelic frequency spectrum also contribute to the risk of developing epilepsy. This so-called oligogenic or polygenic risk of epilepsy has been assessed through common variant signal inferred from genome-wide genotyping arrays and has been reproducibly observed in multiple types of epilepsy (12).

Array comparative genomic hybridization and next-generation sequencing technologies began as research tools and have now become the mainstays of clinical genetic diagnosis in epilepsy (see below). The rapid transition of tools moving from research to clinical diagnostics motivates consideration of the next wave of technological advancements that may further inform the genetic bases of epilepsy on the research level and make their way into clinical practice in the near future. Next-generation sequencing technologies use massively parallel sequencing of short read fragments genome-wide that can be bioinformatically compared to the reference genome to infer genetic variants. While this approach works well for a large portion of the genome, a significant fraction of the genome is missed due to the presence of repetitive regions, complex genomic rearrangements, paralogs, homologs, genomic rearrangements, and difficult to sequencing high G-C rich regions. These complex genomic loci that are largely overlooked with short-read sequencing technology likely harbor epilepsy risk alleles. Long-read sequencing, or third-generation sequencing, allows for the sequencing of DNA fragments at least 100-times longer than short read approaches. This technology offers improved ability to sequence complex regions of the genome and will allow for genotyping of short tandem repeat variants, intermediately sized copy number variants, and complex genomic rearrangements; all types of variants that have, thus far, not been systematically evaluated for their role in epilepsy and other neurodevelopmental disorders.

PARADIGM SHIFT IN THE FIELD

Genetic insights transformed some of the basic concepts of childhood-onset epilepsy. Even before the first specific gene that is associated with epilepsy was identified, it was long predicted that a genetic etiology plays a major role in epilepsy, especially in patients with childhood-onset seizures. During the first decade of the 21st century, the landscape of genetic epilepsy started to take shape with the discovery of genes linked to epilepsy, resulting in advances in the understanding of cellular pathways and pathogenesis. The progress made in understanding the genetic background of epilepsy transformed some prior concepts and assumptions and instructed changes in clinical practice (24, 33). Genetic mechanisms

and inheritance modes that were expected to be rare proved to be common in genetic epilepsies. New pathways and mechanisms of epileptogenesis and targeted interventions were described, and increasing clinical data revealed great heterogeneity of phenotype and genotype associations.

Unexpected in the pre-genomic era, *de novo* pathogenic monogenic variants are now recognized as an important genetic mechanism in epilepsy (2). This is especially common among patients with early onset epileptic encephalopathies. Mosaicism and somatic mutations, rare in other conditions, also play a role in epilepsy (6, 34). X-linked and autosomal recessive inheritance are seen as well.

Learning the clinical presentation of specific genetic epilepsies revealed great variability of genotype-phenotype association (15, 24). Phenotypic heterogeneity is seen with many epilepsy genes; the same gene etiology shows variability of types of seizures and epilepsy syndromes. Epilepsy comorbidities are also variable; the same gene can show variable developmental or intellectual disability or other manifestations. Phenotypic heterogeneity is seen even with the same gene variant within the same family. One individual in the family may show a more severe intractable epilepsy or intellectual disability, while another family member who carries the same variant may show milder manifestations, or different seizure types. Genetic heterogeneity is also seen: the same epilepsy type or epilepsy syndrome is caused by a variety of different genes. Lastly, while it was speculated in the past that generalized epilepsies are genetic while focal epilepsies are likely not, it is now well established that some focal onset epilepsies and some focal brain malformations have genetic etiologies (35).

Clinical availability of genetic testing and rapidly growing knowledge of genetic epilepsy has transformed epilepsy definitions and patient care. Genetic testing is now routinely used in the evaluation of childhood-onset epilepsy and the results directly instruct diagnosis, prognosis, and management decisions (36). The revised International League Against Epilepsy 2017 classification framework emphasizes etiology as part of the classification context, and specifically emphasizes genetic etiology in classification of epilepsy (9). This shift in clinical practice related to epilepsy genetics offers benefits for patient care, and introduces both opportunities and challenges to clinicians and healthcare systems (15).

IMPLICATIONS AND IMPACT ON PATIENT CARE

Evaluation for genetic etiology of childhood-onset epilepsy is routinely used in clinical practice; resulting molecular diagnoses have significant implications and great impact on patient care. High diagnostic yield from genetic testing is seen in early onset epilepsy. In a recent large cohort, positive molecular diagnosis was found in 15 to 24% of tested individuals, and higher proportion was found in specific subsets of patients. Higher diagnostic yield is found in infancy and childhood-onset seizures, infantile epileptic encephalopathy, and in patients with epilepsy and autism, intellectual disability, or developmental disability (37).

Molecular diagnosis has multiple direct benefits, it informs recurrence risk in family members, which may guide reproductive decisions. It also informs prognosis and natural history including risk of complications and multi-systems involvement. This knowledge guides decisions related to monitoring and screening tests,

long-term care plans, and early referral to treatment and support services. Genetic diagnoses frequently have immediate ramifications for clinical decision making for the patients or their relatives (38).

In addition to determining prognosis and recurrence risk, the identification of a genetic etiology can guide anti-seizure treatments. The increasing knowledge of genes and variants associated with epilepsy has direct precision medicine implications. Some genetic epilepsies are now recognized to have specific beneficial antiseizure medications or nonpharmacological treatments. On the other hand, certain medications or treatments are known to exacerbate seizures in a specific genetic disorder and are therefore contraindicated. In addition, some genetic epilepsies involve biochemical pathways that have specific treatments which target the aberrant metabolic etiology (15, 37). New targeted therapeutics are under development, aiming at specific genetic pathways, with a potential to further improve seizure control and health outcomes. Some examples of targeted therapeutics are high dose pyridoxine (vitamin B6) in pyridoxine-dependent epilepsy caused by biallelic pathogenic variants in *ALDH7A1* and everolimus, an mTOR inhibitor, in tuberous sclerosis and other motoropathies, which showed benefit in reducing seizures in epilepsy associated with tuberous sclerosis. Agents such as carbamazepine and lamotrigine are known to exacerbate seizures in patients with SCN1A related Dravet syndrome and therefore are contraindicated. On the other hand, stiripentol, cannabidiol, and fenfluramine show significant benefit for patients with Dravet syndrome. Novel targeted treatments for SCN1A associated epilepsy are now in development, using an anti-sense oligonucleotide (39) (STK-001 phase 1 and phase 2 clinical trials, first posted June 2020 and February 2021, ClinicalTrials.gov identifiers NCT04442295, NCT04740476) and gene transfer interventions (40).

Additional less conspicuous benefits of arriving at a specific diagnosis are the significant psychosocial impacts on patients and families. Confirmation of a molecular diagnosis provides peace of mind, relief from uncertainty, and puts an end to the diagnostic odyssey. Getting to a specific molecular diagnosis reduces the need for diagnostic tests, such as repeated brain imaging and invasive tests. A clear genetic etiology can also provide a sense of relief from the unfounded concern that someone is at fault, or the irrational sense of guilt that some parents feel when making speculations about an epilepsy etiology (24). For example, some parents worry that their child's illness was caused by trauma or drug exposure during pregnancy, or by a minor head injury. Lastly, the benefits of patient and family organizations cannot be overstated. Multiple family organizations and foundations are formed by families and patients with a specific genetic disorder. These groups provide emotional and social support, advocate and sponsor disorder and gene specific research, and create the platform and mechanism to gain specific clinical knowledge and develop clinical trials and gene specific interventions.

EVALUATION PATHWAY

Genetic testing should be considered in any person with childhood-onset epilepsy of unexplained etiology. As discussed above, a genetic diagnosis is important for prognosis and to guide therapies and management for specific genetic

epilepsies (41). Based on chromosome microarray studies, pathogenic copy number variants contribute to 5-10% of the genetic epilepsies. Studies suggest that 30-40% of genetic epilepsies are due to single nucleotide sequence variants including rare recessive inborn errors of metabolism. Additionally, there is an emerging appreciation of the contribution of post-zygotic mutations leading to mosaicisms and brain malformations (contributing to developmental epileptic encephalopathies) as well as variants in noncoding regions of genome (42). Despite rapid advancements in epilepsy neurogenetics currently, approximately 50% of patients with suspected genetic epilepsies remain without a molecular diagnosis (7).

In the 2015 publication summary of recommendations for the management of infantile seizures—Task Force Report for the ILAE Commission of Pediatrics (43)—the Task Force recommends that metabolic disease should be considered in any infant with medication-resistant seizures, or in whom structural or syndromic cause is not evident. In addition, metabolic evaluation should be performed if there is positive family history of epilepsy, specific epilepsy types such as epileptic spasms or early myoclonic epilepsy, neurological regression, encephalopathic episodes, and when there is no structural or infective explanation. The Task Force recommends standard metabolic screening at primary and secondary level care, with glucose, basic hematologic screening, liver function tests, ammonia urine analysis, pH, arterial blood gases, plasma electrolytes, spinal fluid and plasma lactate and glucose. Further metabolic and genetic testing are recommended to be performed by tertiary and quaternary level care and extended genetic screens including next-generation sequencing and linkage analysis. The Task Force specify that:

- Genetic screening should not be undertaken at primary or secondary level care (expert opinion).
- Standard care should permit genetic counseling by trained personal at all levels of care (expert opinion).
- Genetic evaluation for Dravet syndrome, and other infantile-onset epileptic encephalopathies, should be available in tertiary care (weak evidence, level C recommendation).
- Patients should be referred from primary or secondary to tertiary level care after failure of one antiepileptic drug (standard care) and optimal care equates to referral of all infants after presentation with a seizure (expert opinion, level U evidence) (43).

Specific situations are also discussed. The Task Force recommends that genetic testing strategy can vary according to the suspected underlying condition affecting the infant. Examples which are given include full-gene sequencing indicated for conditions such as *SCN1A* for children with febrile seizures plus or Dravet syndrome, karyotype for conditions such as Down syndrome, and whole genome sequencing for a research protocol in an infant with an undiagnosed condition (43).

Since the publication of the Task Force recommendations in 2015, decreasing costs of sequencing resulted in greater availability of epilepsy gene panels for clinical use. These targeted panels test for over 100 genes associated with epilepsy (44). Chromosomal array analysis for copy number variation is used in screening for developmental disability with or without associated seizures. This shift in

availability of genetic testing has initiated a change of practice. Tests for chromosomal copy number variations and epilepsy gene panel may now be considered earlier in the course, if initial evaluation including history, examination, and imaging does not establish a clear etiology, and when genetic etiology is suspected. When genetic tests are ordered prior to referral for evaluation by tertiary/quaternary care facilities, appropriate interpretation, and genetic counseling by trained personal should follow.

CHALLENGES IN GENETIC EVALUATIONS AND TEST INTERPRETATION

Multiple elements are considered in the process of genetic evaluation: selecting the appropriate test for a specific clinical situation; selecting a laboratory best suited to perform the test; interpreting tests results; assessing if the clinical phenotype correlates with results; and, at times, considering the need for further genetic tests or other evaluation.

Selecting a laboratory and test

Selecting the most appropriate test for a patient can be difficult. Additionally, the number of laboratories and available genetic tests is rapidly expanding. All clinical genetic testing should be performed in a laboratory that is fully Clinical Laboratory Improvement Amendments (CLIA) certified and College of American Pathologists (CAP) accredited to ensure the quality of testing is sufficient to their standards. CLIA and CAP accreditation documentation is typically publicly available on the clinical laboratory website.

Performing laboratories may employ genetic counselors that are available to help select the best genetic test. Given their clinical availability, targeted gene panels are typically utilized before performing whole exome or whole genome sequencing. There often is a tendency to gravitate towards a larger gene panel as it has the perception of having a higher diagnostic yield. This is not always the case. The larger panel may include genes that account for less risk of association with genetic epilepsy. There may be many genes that account for a small portion of the diagnostic yield of a genetic test, especially if syndromic etiologies can be ruled out prior to testing (45). Additionally, some panels include genes that have been associated with an increased risk of epilepsy in research settings but have not been described clinically. The clinical contribution of these variants, and thus the interpretation of positive tests, is currently unclear. Discussions with a laboratory genetic counselor may help one select the most appropriate genetic test and reduce the risk of uncertain results.

Interpretation of results

Genetic results are generally categorized into three groups: Positive, Negative, and Uncertain. These categories are determined by how the identified variants are classified, with or without the consideration of the American College of

Medical Genetics and Genomics (ACMG) Variant Curation Guidelines (46). The ACMG guidelines include five classifications: Pathogenic, Likely Pathogenic, Variant of Uncertain Significance, Likely Benign, and Benign. The latter two are not routinely reported by performing laboratories unless requested. Pathogenic and likely pathogenic variants are described as disease-causing variants.

Positive tests results are designated as such when there is a known disease-causing variant in a gene associated with an autosomal dominant condition. Similarly, results are positive if the gene is associated with an autosomal recessive condition and there is either one homozygous disease-causing variant or two compound heterozygous disease-causing variants. Of note, if compound heterozygous variants are identified, it is always advised to test the biological parents to confirm bi-parental inheritance of these variants. If both variants are inherited from the same parent (therefore both gene mutations reside within a single copy of the gene), it would not be considered a positive or diagnostic result (Figure 1). With any positive result, clinical correlation with the condition is suggested.

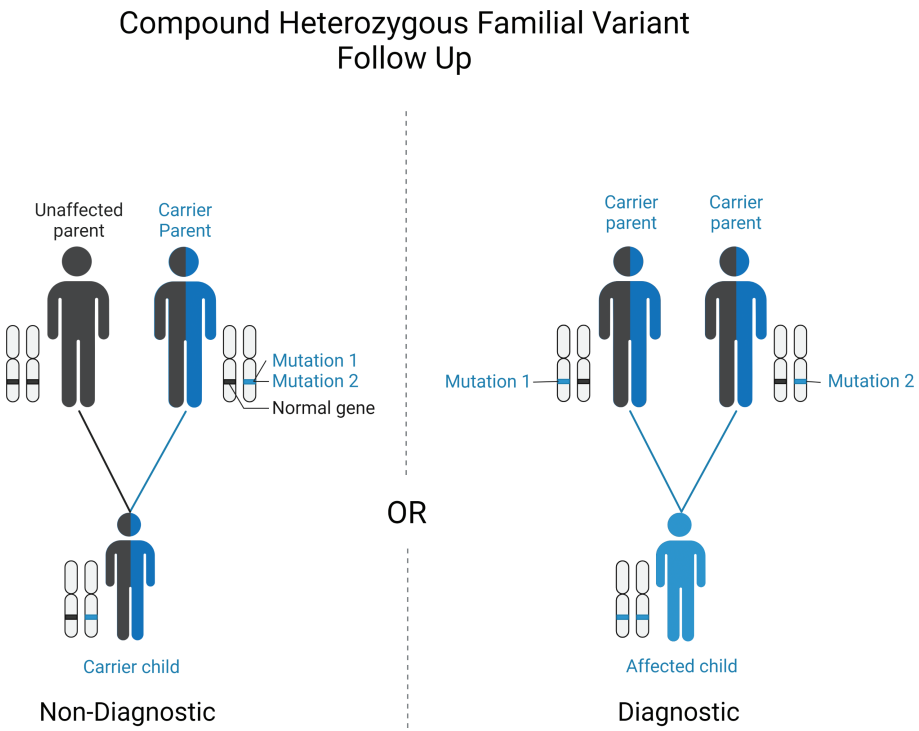

Figure 1. Familial variant testing. Schematic to depict how familial variant testing in one or both biological parents may be informative in the setting of heterozygous, disease-causing variant from a next-generation sequence assay.

When a genetic tests result is reported negative, it is important to understand the limitations of the test. A negative result does not mean there were no variants identified. Often many variants are reviewed but classified as benign or likely benign. A negative result can be a false negative if the assay selected is not able to detect the type of genetic abnormality present in the patient, such as intronic variants or mosaic variants. In patients with a concerning family history and personal history of disease, genetic testing should be revisited as new genes and technologies arise. A negative result can also be reported when a single heterozygous variant is detected for a gene typically associated with an autosomal recessive condition; some labs may consider this a carrier result.

Uncertain results are a possible conclusion for any genetic test. Variants of uncertain significance are not considered diagnostic. When testing for cancer predisposition genes, for example, variants of uncertain significance were reclassified to a benign or likely benign in 94% of cases (47). Contrary to that example, clinical testing for epilepsy gene panels commonly provides uncertain results. A recent report of clinical testing of near 10,000 individuals tested by multi-gene next-generation sequencing (NGS) for epilepsy-related genes found that over 60 percent of tested individuals had an inconclusive report (37). Keeping this in mind, correlating the clinical phenotype to the genetic results can be informative in certain cases. Often, laboratories will suggest parental testing in the report if determining the *de novo* status of the variant would influence the interpretation of the variant. A *de novo* variant is a variant that is present in the patient being tested but absent in the biological parents. If both parents are unaffected, this may warrant additional pathogenic criteria to be applied to the variant and possibly change the classification of the variant.

In addition to familial testing there are some key elements of variant interpretation that should be available within the report to help providers as they evaluate uncertain results:

Variant Frequency in Population Database: Several databases are available that provide information about the frequency of specific gene variants in the general, predominantly healthy, population. The Exome Aggregation Consortium (ExAC) and the Genome Aggregation Database (gnomAD) are the most common publicly accessible databases. Information about the frequency of a specific variant in these or similar databases contributes to the assessment of the clinical significance of the variant. Variants with high frequencies in population databases are less likely to be pathogenic or disease causing. Variants which are rare or absent in population databases are more likely to be a cause of disease.

In silico modeling/predictions: These tools use supervised learning (AI) to predict the variant's impact on the protein by evaluating the DNA sequence and evolutionary conservation as well as the protein sequence and structure-based effects of the variant. Most commonly, SIFT and Poly-Phen-2 are mentioned on reports for variants within the exon boundaries. Some labs may have internal/proprietary in silico models.

Heritability: Assessing whether a variant was inherited from a parent, or arising *de novo*, and considerations of testing of other affected or unaffected family members can add to interpretation of clinical significance of a variant.

Literature and case study publications: Generally, the more publications about a variant the more likely the interpretation will not change as it likely has been described previously. Many variants may be novel or rare enough to be absent from the body of literature the lab is searching. Searching the newest literature for the c. and p. nomenclature in the report may reveal informative literature for further evaluation.

SUGGESTED CLINICAL PRACTICE MODEL

In order to best apply the expanding scientific knowledge of epilepsy genetics to patient care, a new practice model is needed. The new genomic era has transformed clinical practice and offers opportunities for advancement of patient care and epilepsy research. It has also created new demands and challenges for physicians practicing in this rapidly evolving field, who are tasked on a daily basis with applying genetics knowledge to evaluation and management of patients with epilepsy. To best serve their patients, clinicians must consider different testing modalities, be able to interpret test results, and apply the molecular diagnosis to management decisions (15). An example of a frequently encountered challenge is addressing genetic tests showing inconclusive results, such as variants of uncertain significance in genes associated with autosomal dominant disorders, or a heterozygous pathogenic variant in a gene associated with an autosomal recessive disorder (37). Decisions regarding additional genetic tests of the patient or their family members and consulting families regarding ambiguous test results are some of the tasks that clinicians have to address. Input from specialists in epilepsy, genetics, genetic counseling, and laboratory testing specialists is valuable for establishing an evaluation plan, interpreting tests results, and making patient care decisions.

Inspired by daily encounters in our clinical practice, we realize the great opportunities afforded by epilepsy genetics on the one hand, and the clinical challenges on the other. In response, our team of specialists practicing in a tertiary/quaternary academic center, founded The University of North Carolina Epilepsy Neurogenetics Initiative (ENGI). A collaboration of clinicians specialized in child neurology, genetics, genetic counseling, and researchers, teamed to work for the common goal to leverage advances in epilepsy genetics to improve health outcomes. The ENGI's vision is to apply the rapidly expanding knowledge of epilepsy genetics to clinical practice and maximize the benefits of scientific advancements in patient care. The ENGI includes a comprehensive multidisciplinary clinical care program and research partnerships that serve as the foundation for clinical and translational research. ENGI Clinical Core aims are to provide specialized care to our patients with genetic epilepsy, to improve the process and efficiency of genetic testing in childhood-onset epilepsy, and to standardize and continuously update epilepsy genetics evaluations processes. We prepare individualized treatment plans for each of our patients with the guidance of our multidisciplinary team of experts who discuss management plans during our bi-monthly neurogenetics meetings. We find that these multidisciplinary meetings are an efficient and effective platform for developing evaluation and management plans. We offer patient and family-centered care for patients with known or suspected genetic

epilepsy syndromes, for patients with unclear or non-diagnostic genetic testing results, and for patients with epilepsy with a prior genetic diagnosis that requires additional evaluation.

ENGI Research Core is a partnership between clinicians, research collaborators, and basic scientists to study best practices and guide future implementation of genomic technologies. Basic science collaborations aim to improve the understanding of cellular, molecular, and nervous system functions underlying epilepsy genetics and to identify pathogenic gene variants and candidate risk genes. The overall goal of the ENGI Research Core is to assist in identifying targeted therapies, as our rapidly advancing field moves towards finding cures for patients with genetic epilepsies. The Research Core assists in providing patients with state-of-the-art care by improving patient access to clinical trials and translational research, connecting families to local, regional, and national studies, and linking patients to genetic-specific treatment clinical trials. The program is also committed to training the next generation of doctors to provide care for children with known or suspected genetic epilepsies and offers educational opportunities for students and physicians. ENGI's outreach program continues to develop a regional referral base and serves as a resource for physicians, patients, and families.

CONCLUSION

The rapidly evolving field of epilepsy genetics is transforming clinical practice, providing exciting new targets for development of novel therapies, and is an example of rapid implementation of precision medicine into daily clinical practice and patient care. Advancements in this field are likely to continue to impact future changes, and better the life of people living with genetic epilepsies.

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