Molecular Genetics of Epilepsy: A Clinician's Perspective

Vikas Dhiman
Department of Neurology, Ivy Hospital, Panchkula, Haryana, India

Abstract

Epilepsy is a common neurological problem, and there is a genetic basis in almost 50% of people with epilepsy. The diagnosis of genetic epilepsies makes the patient assured of the reasons of his/her seizures and avoids unnecessary, expensive, and invasive investigations. Last decade has shown tremendous growth in gene sequencing technologies, which have made genetic tests available at the bedside. Whole exome sequencing is now being routinely used in the clinical setting for making a genetic diagnosis. Genetic testing not only makes the diagnosis but also has an effect on the management of the patients, for example, the role of sodium channels blockers in *SCN1A*+ Dravet syndrome patients and usefulness of ketogenic diet therapy in *SLC2A1*+ generalized epilepsy patients. Many clinicians in our country have no or limited knowledge about the molecular genetics of epilepsies, types of genetic tests available, how to access them and how to interpret the results. The purpose of this review is to give an overview in this direction and encourage the clinicians to start considering genetic testing as an important investigation along with electroencephalogram and magnetic resonance imaging for better understanding and management of epilepsy in their patients.

Keywords: Clinical, epilepsy, genetics, molecular

Introduction

Epilepsy is the most common serious neurological disorder, affecting around 65 million people in the world.[1] In more than 50% of people with epilepsy (PWE), the cause of seizures is not known.[2] These types of epilepsies were designated as "idiopathic" in the 1989 seizure classification.[3] With rapid advancements in the molecular genetic techniques, our understanding about idiopathic epilepsies has improved exponentially. More than half of all epilepsies are now known to have a genetic basis. This led the International League Against Epilepsy (ILAE) to replace the term idiopathic epilepsies with "genetic generalized epilepsies."[4] Epilepsies due to structural lesions, such as focal cortical dysplasia, hippocampal sclerosis, and encephalopathies, were once thought to be solely due to structural pathology, but recently, more and more evidence supporting the genetic basis of these epilepsies is readily available in the literature.[1,5] These rapid developments in the molecular genetics of epilepsy have changed the way we think about the causes of epilepsies, and it is bound to have an impact on the diagnosis and management of PWE. Whole exome sequencing (WES) is proving to be a highly effective method in identifying a causative gene in the clinical setting.[6] In the present times, everyone involved in the management of epilepsy patients, especially the clinician should have some grounding information about epilepsy genetics.

The main objectives of this review are to provide (a) clinically relevant aspects of molecular genetics of commonly encountered genetic epilepsies; (b) the clinical implications of this knowledge in pharmacogenetics, clinical genetic testing, and the management of PWE; and (c) the future prospects and challenges in the field.

What are Genetic Epilepsies?

The ILAE Commission on Classification and Terminology (2005–2010) defined genetic epilepsies as in which seizures occur as a result of a known or presumed genetic defect (s).[4] More than twenty genes are known to have a major susceptibility to "idiopathic" epilepsies.[7] Like most complex disorders, both genetic and environmental factors contribute in the disease phenotype expression, but the scientific evidence in the support of latter is not as robust as the former in case of

Address for correspondence: Dr. Vikas Dhiman, House No. 54/2, Subhash Nagar, Manimajra, Chandigarh - 160 101, India.
E-mail: vickylepsy@gmail.com

Access this article online

Quick Response Code:

Website: www.annalsofian.org

DOI: 10.4103/aian.AIAN_447_16

How to cite this article: Dhiman V. Molecular genetics of epilepsy: A clinician's perspective. Ann Indian Acad Neurol 2017;20:96-102.

epilepsies.[4] There is a continuum spectrum of phenotype of genetic epilepsies seen, ranging from monogenic epilepsies with no (or minimal) environmental effect on the one hand to complexly inherited polygenic epilepsies on the other end.[7] Most of the genetic epilepsies lie in the gray zone in between [Figure 1]. One way of classifying most genetic epilepsy syndromes is by their age of presentation.[8,9] The following paragraph gives a brief outlook on the most common genetic epilepsies encountered in the clinical practice (with causative gene in italics). The detailed clinical description of these epilepsies can be found elsewhere.

The genetic epilepsies seen during the 1st year of life are benign familial neonatal seizures (BFNS) (*KCNQ2* and *KCNQ3*), benign familial neonatal-infantile seizures (*SCN2A*), and benign familial infantile seizures.[10] These are autosomal dominant epilepsy syndromes characterized by onset of seizures before first birthday and have a strong positive family history.[10,11] Other epilepsies with more complex pattern of inheritance in this age group include Ohtahara syndrome (*STXBPI* and *ARX*), West syndrome, and Dravet syndrome (*SCN1A*).[6,12] Febrile seizures affect 3% of children between age group of 6 months and 6 years.[13] Genetic epilepsy with febrile seizure plus (*SCN1A, SCN1B,* and *GABRG2*) and Dravet syndrome (*SCN1A*) form an important differential diagnosis, especially in a child with febrile seizures and developmental delay.[6,12]

In childhood, classic generalized epilepsies, for example, childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and epilepsy with generalized tonic–clonic seizures, which form about 20% of all epilepsies, are more common.[14] Although the genetic basis of most of these epilepsies remains elusive, early onset absence epilepsy (*SLC2A1*) and JME (*GABRA1* and *EFHC1*) have a stronger genetic basis.[14] Partial epilepsies have long been associated with focal structural lesions. The genetic linkage analysis in multiplex families with partial epilepsies has identified various causative genes, for example, autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) (*CHRNA4, CHRNB2,* and *CHRNA2*),[15] autosomal dominant epilepsy with auditory features (*LGI1*),[16] familial temporal lobe epilepsies (FTLE), and familial focal epilepsy with variable foci (FFEVF) (*DEPDC5*).[17] Progressive epileptic syndromes such as progressive myoclonus epilepsies (Unverricht–Lundborg disease, *CSTB* and Lafora body disease, *EPM1* and *EPM2*) are also now known to have a strong genetic basis.[18] In the past few decades, genetics have also been implicated in various nonsyndromic epilepsies like those caused by structural and/or metabolic reasons, for example, malformations of cortical development (lissencephaly, *PAFAH1B1,* and *DCX*), neurocutaneous syndromes (tuberous sclerosis, *TSC1* and *TSC2*), tumors, infections, brain trauma, and perinatal insults.[19,20]

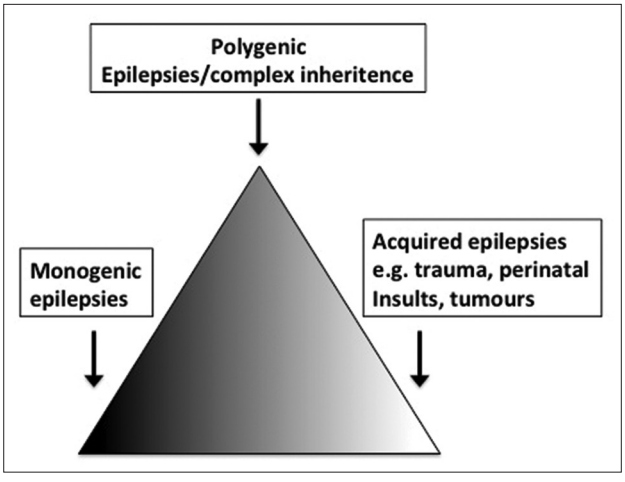

Figure 1: Spectrum of genetic epilepsies (original)

Clinically speaking, there are multiple indicators of genetic epilepsies.[21] On the one hand, genetic epilepsy should be suspected in a patient with early awakening seizures, normal neurological and imaging findings, 3 Hz spike and wave discharges on electroencephalogram, and a positive family history of seizures and when no underlying cause of seizures is demonstrable.[22] Various previously designated "idiopathic" generalized epilepsies such as JME, JAE, CAE, and epilepsy with generalized tonic–clonic seizures only, fall in this category. On the other hand, a genetic cause is strongly suspected in a patient with seizures with early age of onset (infantile or childhood), seizures associated with congenital anomaly, developmental delay, or autism spectrum disorder with or without positive family history of seizures.[21] Examples in this category included various epileptic encephalopathies (e.g., Ohtahara syndrome, West syndrome, and Dravet syndrome), cortical dysplasias, and neurocutaneous syndromes (e.g., tuberous sclerosis). There are separate sets of genetic tests available for these two groups (see genetic testing and implications).

Molecular Mechanisms: Underlying Cause of Seizures

The purpose of this section is to give a clinically relevant conceptual understanding of the underlying molecular basis of seizure occurrence rather enlisting every gene that has so far been linked to epilepsy. Every protein in our body is synthesized from their genes through the process of transcription (formation of messenger RNA, mRNA) and translation (synthesis of protein from mRNA). Factors which do not necessarily change the structure of the gene but do affect the process of transcription and translation are known as epigenetic factors.[23] Any perturbation in the transcription, translation, or epigenetic mechanisms can produce defective proteins leading to diseases. Seizures occur as a result of a complex interplay of altered gene expressions, increased neuronal excitability and disturbed intrinsic neuronal properties.[5,24] Defects in epilepsy genes give a critical insight into the pathomechanisms of seizure generation and propagation, which has an impact on the management of the patients[25] as illustrated below.

Voltage-gated sodium channels are an important group of ions channels, which play an important role in generating action potential and depolarization of the neurons. Dravet syndrome, previously known as severe myoclonic epilepsy of infancy, is caused by mutations in the alpha 1 subunit of the voltage-gated sodium channel gene, *SCN1A*.[6] It is characterized by the onset of febrile seizures before 7 months of age, prolonged seizure episodes (>10 min), and developmental delay during 2nd year of life.[6] About 70%–80% of patients with Dravet syndrome have mutations in *SCN1A* gene. This mutation in *SCN1A* gene causes defective gating in the sodium channel and thus causes hyperexcitability and seizures.[13] Different mutations (genotypes) produce different phenotypes (see below). *SCN1A*-positive Dravet syndrome patients have an important implication in the pharmacological management – all antiepileptic drugs (AEDs) with a dominant action on sodium channels (phenytoin, carbamazepine, oxcarbazepine, lamotrigine, and vigabatrin) can interfere with gating mechanism of the mutated channels and increase the frequency of seizures, especially myoclonic seizures in patients with Dravet syndrome, thus these AEDs can exacerbate seizures and thus should be avoided.[12]

Patients with early onset absence epilepsy, paroxysmal exertional dyskinesia, and encephalopathies are found to have mutations in *SLC2A1* gene, which leads to GLUT1 deficiency.[26] GLUT1 protein transports glucose in the neurons from blood and surrounding cells. Mutations in *SLC2A1* gene reduce or eliminate the function of the GLUT1 protein. It has been observed that patients with GLUT1 deficiency (*SLC2A1* mutations) show a remarkable reduction in seizure frequency following ketogenic diet therapy.[27] Although the underlying mechanisms of how ketogenic diet ameliorates seizures are not known, knowing that less functional GLUT1 protein reduces the amount of glucose available to brain cells, ketogenic diet has a role to play in seizure termination in these patients. These findings have relegitimized ketogenic diet therapy in epilepsy patients. Hence, all patients with GLUT1 deficiency should be considered for early trials of ketogenic therapy.[27,28]

Genotype–phenotype Correlation

Genotype–phenotype correlations always pose a problem for complex disorders such as epilepsy, diabetes, hypercholesterolemia, and hypertension.[2,7] Due to complex genotype–phenotype correlations, classification and categorization of diseases become difficult. Epilepsy genes have been shown to carry all types of mutations, from missense to frameshift mutations to chromosomal aberrations and copy number variations, which account for phenotypic heterogeneity seen in epilepsy.[29] There are multiple tests available in the market, which can identify each of these mutations (see genetic testing and implication). It is general dictum is that the larger the mutation, the more severe is the phenotype,[12] but this does not hold true always. One of the important reasons for poor genotype–phenotype correlation in epilepsies is that most of the epilepsies have a complex pattern of inheritance with involvement of two or more genes and variable environmental effects; even same type of mutation in two individuals can express disease with variable severity.[30] For example, the mutation of *KCNQ2* can cause a benign BFNS in some neonates and severe epileptic encephalopathies in others.[31]

However, the entire scenario is not that gloomy too. It has been observed that many well-defined mutations cause a specific phenotype, for example, patients with truncating mutations in *SCN1A* gene lead to earlier onset of seizures in patients with Dravet syndrome than those with missense mutations.[30,32] Furthermore, it has been noted that micro-chromosomal rearrangements involving *SCN1A* gene and contiguous genes are potentially associated with additional dysmorphic features in the affected patients.[32] It is interesting to note that in a patient in whom all sodium channels genes along with 49 contiguous genes were deleted, did not show any phenotype distinct from typical Dravet syndrome.[30] There are few important points, which a clinician should know when attempting a genotype–phenotype correlation in a case of epilepsy:

a. The clinical profile (demography, clinical signs and symptoms, and investigation's results) should be clearly understood
b. The genetic diagnosis, genetic technique employed, and its limitations should be understandable to the clinician
c. A detailed family (at least three generation) should be drawn in case of positive family history
d. The clinician should try to rule out any possible environmental effect, variable penetrance, and mosaicism
e. Be open-minded and discuss with clinical geneticist, if required.

Role of Pharmacogenetics

Pharmacogenetics deals with studying genetic variations among individuals, which affect the response to medications. With rapid advancements in the genomics and pharmacology, it is now possible to predict the differences in treatment outcomes in patients with apparently same disease and treatment by studying the genetic sequence variations between patients. These genetic sequence variations or polymorphisms have a profound effect on drug absorption, transport, metabolism, clearance, and site of action.[33] Furthermore, individuals with specific polymorphism are susceptible to adverse drug reactions. Pharmacogenetics has the potential to identify these susceptible individuals before treatment and selectively allow patients with low risk of adverse drug reactions for pharmacological management.[33]

In epilepsy, pharmacogenetics plays a very important role, especially in pharmacoresistance to seizures, unpredictability of AEDs response, and idiosyncratic drug reactions.[34,35] Numerous genetic association studies have identified various genes, which are implicated in AED transport (Multidrug-resistant protein/adenosine triphosphate-binding cassette protein, *MDR1/ABCB1*, *MDR2/ABCB2*), metabolizing enzymes (cytochrome P450, *CYP2D6, CYP3A4, CYP2C9, CYP2C19,* and *CYP2E1;*

glucuronosyltransferase, *UGT1A6 and UGT1A9*), ion channels (*SCN1A*), and immune system (*HLA-DR, HLA-DQ,* and *HLA-B*).[36,37] P-glycoprotein is a drug efflux transporter, which is associated with *MDR1/ABCB1* gene. Commonly used AEDs phenytoin and valproic acid are known to inhibit P-glycoprotein expression, making it a potential target for pharmacoresistance.[36] Cytochrome P450 liver enzymes metabolize most AEDs. Genetic variations in these enzymes can alter the metabolism and clearance of the AEDs from the body. For example, individuals with poor metabolizer allele of *CYP2C9* or *CYP2C19* genes need lower doses of phenytoin to achieve optimum serum level as compared to an individual with normal allele. The identification of such genotype can prevent unnecessary phenytoin toxicity in the patients.[38]

Many AEDs such as phenytoin, carbamazepine, and lamotrigine act through voltage-gated sodium channels (*SCN1*). Mutations in the alpha subunit of sodium channels (*SCN1A*) have been known to cause febrile seizures and Dravet syndrome in children.[30] It has been shown that patients with AA genotype in *SCN1A* gene required higher doses of phenytoin and carbamazepine for seizure control than those patients who had GG genotype.[32] Adverse drug reactions such as cutaneous hypersensitivity reactions are common with AEDs. Pharmacogenetics has the potential to reduce up to 50% of adverse drug reaction in PWE treated with AEDs.[34] This is best exemplified by *HLA-B*1502* allele on the major histocompatibility complex strong association with AED-induced Steven–Johnson syndrome/ toxic epidermal necrolysis (SJS/TEN) in Asian patients.[39] Similar association has also been seen with *HLA-A*3101* with carbamazepine-induced cutaneous reactions but the follow-up studies failed to show the results consistently.[40] As of now, testing *HLA-B*1502* allele before starting AED treatment in Asian patients is the only clinically relevant testing available.

Genetic Testing and Implications

It is important to take the advancements in epilepsy genetics from bench to bedside. As stated previously, the basis of most of the common genetic epilepsies is multifactorial with both genetic and environmental factors playing major roles, but nevertheless, there are multiple genetic tests available in the market to make diagnosis of specific type of epilepsy syndromes. Genetic testing in PWE is done mainly in two scenarios, first, where the patient is already known or suspected to have epilepsy and second, to predict the occurrence of epilepsy in a person with a family history of epilepsy.[22] The latter situation is commonly encountered, and the knowledge of percentage risk of manifesting a diseases in different modes of genetic inheritance would be useful for clinicians in day-to-day practice. In autosomal dominant epilepsies, for example, BFNS, BFIS, ADNFLE, FTLE, and FFEVF, there is a 50% chance of passing the mutated gene in each child. In autosomal recessive epilepsy syndromes such as Unverricht-Lundborg disease, Lafora disease, and dentatorubral-pallidoluysian atrophy, both parents with carrier mutation can pose a 25% risk of exhibiting the disease in every pregnancy. The chance of having an unaffected child but carrier of the disorder is 50%, and the chance that a child is both unaffected and not a carrier is 25%. The mode of inheritance of febrile seizures in children is more complex. Various family and twin studies have reported that the risk of siblings of the affected child is between 10% and 20%.[32,41] Many epileptic encephalopathies have been recently found to have *de novo* mutations, wherein a new genetic mutation occurs in the individual with no history of disorder in either of parents.[42]

There is rapid mushrooming of genetic testing facilities across the country, but it is very important to note that the clinical genetic testing must be done in a certified genetic laboratory equipped with quality control standards, accurate methods to interpret results, and the facility to offer genetic counseling to the patient and family members. An attempt should be made to make an accurate clinical diagnosis before requesting a genetic test in a patient with epilepsy, and in doing so, additional information such as detailed family history, laboratory parameters, and associated disorders help. The genetic tests available for a clinician in epilepsy patients are array comparative genomic hybridization (aCGH) for detecting copy number variants, sanger sequencing for screening candidate genes and next generation sequencing (NGS), or massively parallel sequencing for gene panels. aCGH is usually a first-line investigation in patients with an epilepsy syndrome, for example, seizures associated with facial and bodily dysmorphism, congenital malformations, intellectual disabilities, or psychiatric problems.[22,43] NGS technologies allow screening of as many genes as possible in clinical setting in patients with epilepsy, particularly in patients with highly heterogeneous epileptic syndromes. As per the ILAE Genetics Commission report,[22] the most useful genes in epilepsy patients in the clinical testing are listed in Table 1. A clinically useful flowchart-based approach to genetic testing in common genetic epilepsies is shown in Figure 2. The list of the genes is not complete as the field of epilepsy genetics is moving rapidly, and more and more new genes are expected to add-in in the coming times.

Genetic testing has important psychological, social, and financial implications.[22,43] Knowing the genetic basis of their disease makes the patient relieved about the diagnosis and prevents them from undergoing unnecessary, laborious, invasive, and often expensive investigations. It is important to note that a positive genetic test can also cause psychological stress and fear among patients and family members, which sometimes lead to discrimination in employment and society.[2] Thus, it is important to have a pre- and post-genetic test counseling by a trained genetic counselor.[2] Another important clinical implication is in marriage and reproductive decisions. Genetic testing is usually advised in people where there is strong family history of genetic epilepsies, or parents share a common genetic pool (consanguineous marriage).[22] The chances of developing a recessive disorder are higher if both parents share a common ancestry. Therefore, it is important to get genetic counseling and testing done in such

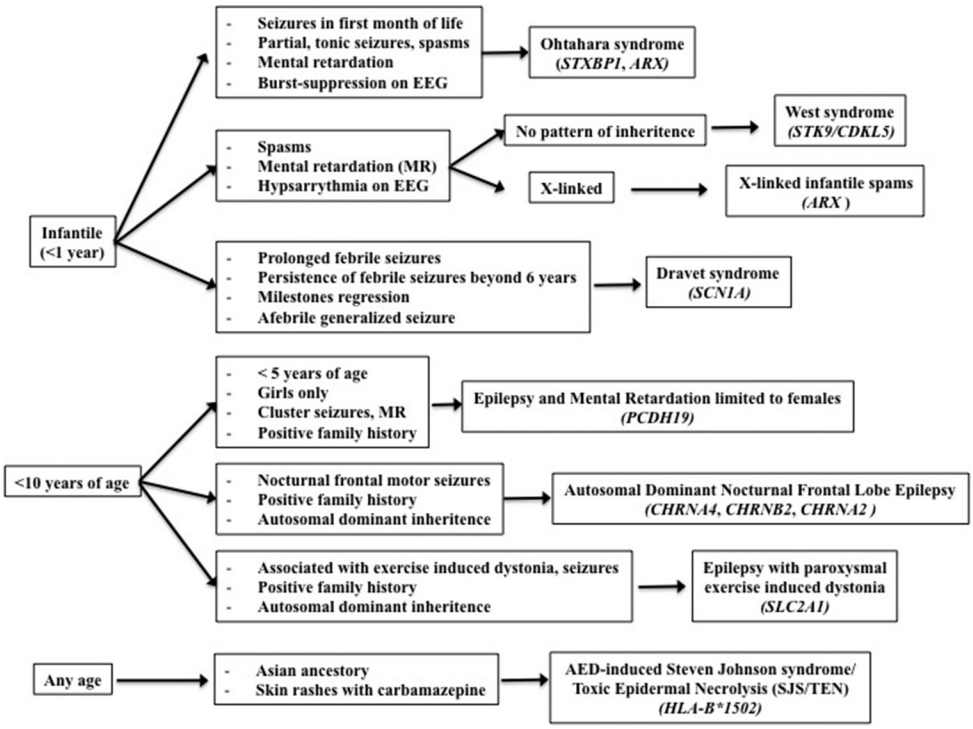

Figure 2: Flowchart-based approach to genetic testing in common genetic epilepsies (original)

Table 1: Clinically most useful genes for genetic testing in epilepsy patients

Gene implicated	Epilepsy syndrome
STXBP1	Ohtahara syndrome
ARX	
STK9/CDKL5	Early onset spasms
ARX	X-linked infantile spasms
SCN1A	Dravet syndrome or severe myoclonic epilepsy of infancy
PCDH19	Epilepsy and mental retardation limited to females
CHRNA4	ADNFLE
CHRNB2	
CHRNA2	
SLC2A1	Epilepsy with paroxysmal exercise-induced dyskinesia
*HLA-B*1502*	AED-induced SJS/TEN, before starting AED in Asian patients

SJS/TEN = Steven-Johnson syndrome/toxic epidermal necrolysis, ADNFLE = Autosomal dominant frontal lobe epilepsy, AED = Antiepileptic drug

couples before marriage and conception.[22] Another aspect of genetic testing is the cost-effectiveness.[44] The high cost of genetic testing has some limitations in less developed countries like India, but with rapid progress in gene sequencing technologies and wider availability, the cost of genetic testing is going to reduce in the coming years.[45]

Indian Scenario

There have been multiple epilepsy genetics studies in India, focusing from pharmacogenomics to familial studies in JME and CAE. Contrary to multiple studies[46-48] showing association of *ABCB1/MDR1* gene polymorphism in drug-resistant epilepsy, no such association is observed in the Indian population,[49] although significant involvement of *CYP2C9*, *SCN2A,* and *GABRA* genetic variants in modulation of epilepsy pharmacotherapy has been observed in the North Indian population.[50,51] Association between polymorphism of a neuronal signaling molecule, namely, reelin (*RELN*) has also been seen with childhood epilepsy in Eastern Indian population from West Bengal.[52] Numerous family-based genetic association studies have been done in India, especially in JME. A locus for JME has been mapped to 2q33-q36 and 5q12-q14 in South Indian population.[53] Similarly, the absence of *GABRA1* Ala 322Asp mutation has been noted in JME families from South India.[54] In addition, IGE syndrome is found to be linked to 3q13.3-q21 and missense mutation in the extracellular calcium-sensing receptor gene in the Indian population.[55] Another large family study showed a linkage of familial childhood absence seizures to chromosome 8q24.[56]

Future Prospects and Challenges

The advancements in molecular genetics of epilepsy have propelled the epilepsy research to an all-time high. Recent discoveries of epilepsy genes have definitely increased our understanding of epilepsies and their clinical management, but one important development that will guide future research is the role of molecular pathways that cause seizure disorders. This is best exemplified by recent advancement in the understanding of mammalian target of rapamycin pathway in the pathophysiology of epileptic encephalopathies and development of rapamycin as

its therapeutic target.[24,25] WES/whole genome sequencing has made genetic tests accessible at the bedside. Newer methods and techniques such as cerebral organoids, induced pluripotent stem cells, and gene editing (e.g., clustered regularly interspaced short palindromic repeats) will generate new data that will challenge our long-held concepts about pathomechanisms of epilepsies.[57-59] These newer approaches have the potential to unravel the most complex genetic mechanisms underlying epileptic seizures.

With a lot good holding in the future in epilepsy genetics, there are few challenges, which the epilepsy community has to work together and find solutions. Complex genotype–phenotype correlations will continue to haunt the epilepsy scientists. Large multinational consortium studies following uniform diagnostic guidelines will generate huge data, which will be more valid and acceptable and help in making more accurate genotype–phenotype predictions. In a less developed country like India, the genetic testing may not be easily available for every strata of society. It is expected that with further improvements in sequencing technologies, the cost of NGS for single gene/panel testing will reduce drastically, helping NGS to become a routinely employed diagnostic tool. The clinicians and resident doctors should be encouraged to take a detailed family history during patient evaluation, a lack of adequate family history leads to wrong diagnosis and management. Inadequate family history underestimates the utility of genetic testing in clinical practice. A professional, accurate, and effective counseling by a trained genetic counselor is an important cornerstone in the management of patients with genetic epilepsies; unfortunately, there is an acute shortage of genetic counselors in the country. With genetic tests going to become a routine laboratory investigation in coming times, this shortage of genetic counselors should be promptly dealt with.

Financial support and sponsorship

Nil.

Conflict of interest

There are no conflicts of interest.

References

1. Moshé SL, Perucca E, Ryvlin P, Tomson T. Epilepsy: New advances. Lancet 2015;385:884-98.
2. Pal DK, Pong AW, Chung WK. Genetic evaluation and counseling for epilepsy. Nat Rev Neurol 2010;6:445-53.
3. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1989;30:389-99.
4. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, *et al.* Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 2010;51:676-85.
5. Mirza N, Appleton R, Burn S, Carr D, Crooks D, du Plessis D, *et al.* Identifying the biological pathways underlying human focal epilepsy: From complexity to coherence to centrality. Hum Mol Genet 2015;24:4306-16.
6. Veeramah KR, Johnstone L, Karafet TM, Wolf D, Sprissler R, Salogiannis J, *et al.* Exome sequencing reveals new causal mutations in children with epileptic encephalopathies. Epilepsia 2013;54:1270-81.
7. Thomas RH, Berkovic SF. The hidden genetics of epilepsy – A clinically important new paradigm. Nat Rev Neurol 2014;10:283-92.
8. Blume WT, Lüders HO, Mizrahi E, Tassinari C, van Emde Boas W, Engel J Jr. Glossary of descriptive terminology for ictal semiology: Report of the ILAE task force on classification and terminology. Epilepsia 2001;42:1212-8.
9. Berg AT, Cross JH. Towards a modern classification of the epilepsies? Lancet Neurol 2010;9:459-61.
10. Zara F, Specchio N, Striano P, Robbiano A, Gennaro E, Paravidino R, *et al.* Genetic testing in benign familial epilepsies of the first year of life: Clinical and diagnostic significance. Epilepsia 2013;54:425-36.
11. Muntoni F, Cross JH. Paediatric neurology: From molecular mechanisms to targeted treatments. Lancet Neurol 2015;14:16-8.
12. Lemke JR, Riesch E, Scheurenbrand T, Schubach M, Wilhelm C, Steiner I, *et al.* Targeted next generation sequencing as a diagnostic tool in epileptic disorders. Epilepsia 2012;53:1387-98.
13. Nabbout R, Prud'homme JF, Herman A, Feingold J, Brice A, Dulac O, *et al.* A locus for simple pure febrile seizures maps to chromosome 6q22-q24. Brain 2002;125(Pt 12):2668-80.
14. Guerrini R. Epilepsy in children. Lancet 2006;367:499-524.
15. Becchetti A, Aracri P, Meneghini S, Brusco S, Amadeo A. The role of nicotinic acetylcholine receptors in autosomal dominant nocturnal frontal lobe epilepsy. Front Physiol 2015;6:22.
16. Michelucci R, Pasini E, Nobile C. Lateral temporal lobe epilepsies: Clinical and genetic features. Epilepsia 2009;50 Suppl 5:52-4.
17. Picard F, Makrythanasis P, Navarro V, Ishida S, de Bellescize J, Ville D, *et al.* DEPDC5 mutations in families presenting as autosomal dominant nocturnal frontal lobe epilepsy. Neurology 2014;82:2101-6.
18. Kälviäinen R, Khyuppenen J, Koskenkorva P, Eriksson K, Vanninen R, Mervaala E. Clinical picture of EPM1-Unverricht-Lundborg disease. Epilepsia 2008;49:549-56.
19. Cardoso C, Leventer RJ, Dowling JJ, Ward HL, Chung J, Petras KS, *et al.* Clinical and molecular basis of classical lissencephaly: Mutations in the LIS1 gene (PAFAH1B1). Hum Mutat 2002;19:4-15.
20. Guerrini R, Marini C. Genetic malformations of cortical development. Exp Brain Res 2006;173:322-33.
21. Mefford HC. Clinical genetic testing in epilepsy. Epilepsy Curr 2015;15:197-201.
22. Ottman R, Hirose S, Jain S, Lerche H, Lopes-Cendes I, Noebels JL, *et al.* Genetic testing in the epilepsies – Report of the ILAE Genetics Commission. Epilepsia 2010;51:655-70.
23. Kobow K, El-Osta A, Blümcke I. The methylation hypothesis of pharmacoresistance in epilepsy. Epilepsia 2013;54 Suppl 2:41-7.
24. Staley K. Molecular mechanisms of epilepsy. Nat Neurosci 2015;18:367-72.
25. Noebels J. Pathway-driven discovery of epilepsy genes. Nat Neurosci 2015;18:344-50.
26. Gardiner AR, Jaffer F, Dale RC, Labrum R, Erro R, Meyer E, *et al.* The clinical and genetic heterogeneity of paroxysmal dyskinesias. Brain 2015;138(Pt 12):3567-80.
27. Larsen J, Johannesen KM, Ek J, Tang S, Marini C, Blichfeldt S, *et al.* The role of SLC2A1 mutations in myoclonic astatic epilepsy and absence epilepsy, and the estimated frequency of GLUT1 deficiency syndrome. Epilepsia 2015;56:e203-8.
28. Gumus H, Bayram AK, Kardas F, Canpolat M, Çaglayan AO, Kumandas S, *et al.* The effects of ketogenic diet on seizures, cognitive functions, and other neurological disorders in classical phenotype of glucose transporter 1 deficiency syndrome. Neuropediatrics 2015;46:313-20.
29. Loeb JA. Identifying targets for preventing epilepsy using systems biology. Neurosci Lett 2011;497:205-12.
30. Marini C, Scheffer IE, Nabbout R, Mei D, Cox K, Dibbens LM, *et al.* SCN1A duplications and deletions detected in Dravet syndrome: Implications for molecular diagnosis. Epilepsia 2009;50:1670-8.
31. Weckhuysen S, Mandelstam S, Suls A, Audenaert D, Deconinck T, Claes LR, *et al.* KCNQ2 encephalopathy: Emerging phenotype of a neonatal epileptic encephalopathy. Ann Neurol 2012;71:15-25.
32. Hirose S, Scheffer IE, Marini C, De Jonghe P, Andermann E, Goldman AM, *et al.* SCN1A testing for epilepsy: Application in clinical practice. Epilepsia 2013;54:946-52.

33. Löscher W, Klotz U, Zimprich F, Schmidt D. The clinical impact of pharmacogenetics on the treatment of epilepsy. Epilepsia 2009;50:1-23.
34. Szoeke CE, Newton M, Wood JM, Goldstein D, Berkovic SF, OBrien TJ, *et al.* Update on pharmacogenetics in epilepsy: A brief review. Lancet Neurol 2006;5:189-96.
35. Johnson MR, Tan NC, Kwan P, Brodie MJ. Newly diagnosed epilepsy and pharmacogenomics research: A step in the right direction? Epilepsy Behav 2011;22:3-8.
36. Budi T, Tóth K, Nagy A, Szever Z, Kiss Á, Temesvári M, *et al.* Clinical significance of CYP2C9-status guided valproic acid therapy in children. Epilepsia 2015;56:849-55.
37. Manna I, Gambardella A, Labate A, Mumoli L, Ferlazzo E, Pucci F, *et al.* Polymorphism of the multidrug resistance 1 gene MDR1/ABCB1 C3435T and response to antiepileptic drug treatment in temporal lobe epilepsy. Seizure 2015;24:124-6.
38. Chung WH, Chang WC, Lee YS, Wu YY, Yang CH, Ho HC, *et al.* Genetic variants associated with phenytoin-related severe cutaneous adverse reactions. JAMA 2014;312:525-34.
39. Chen P, Lin JJ, Lu CS, Ong CT, Hsieh PF, Yang CC, *et al.* Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. N Engl J Med 2011;364:1126-33.
40. Wen ZP, Fan SS, Du C, Yin T, Zhou BT, Peng ZF, *et al.* Influence of acylpeptide hydrolase polymorphisms on valproic acid level in Chinese epilepsy patients. Pharmacogenomics 2016;17:1219-25.
41. Scheffer IE, Berkovic SF. Generalized epilepsy with febrile seizures plus. A genetic disorder with heterogeneous clinical phenotypes. Brain 1997;120(Pt 3):479-90.
42. EpiK Consortium; Epilepsy Phenome/Genome Project, Allen AS, Berkovic SF, Cossette P, Delanty N, Dlugos D, *et al. De novo* mutations in epileptic encephalopathies. Nature 2013;501:217-21.
43. Helbig I, Mefford HC, Sharp AJ, Guipponi M, Fichera M, Franke A, *et al*. 15q13.3 microdeletions increase risk of idiopathic generalized epilepsy. Nat Genet 2009;41:160-2.
44. Leu C, Coppola A, Sisodiya SM. Progress from genome-wide association studies and copy number variant studies in epilepsy. Curr Opin Neurol 2016;29:158-67.
45. Jiang T, Tan MS, Tan L, Yu JT. Application of next-generation sequencing technologies in Neurology. Ann Transl Med 2014;2:125.
46. Siddiqui A, Kerb R, Weale ME, Brinkmann U, Smith A, Goldstein DB, *et al.* Association of multidrug resistance in epilepsy with a polymorphism in the drug-transporter gene ABCB1. N Engl J Med 2003;348:1442-8.
47. Seo T, Ishitsu T, Ueda N, Nakada N, Yurube K, Ueda K, *et al.* ABCB1 polymorphisms influence the response to antiepileptic drugs in Japanese epilepsy patients. Pharmacogenomics 2006;7:551-61.
48. Maleki M, Sayyah M, Kamgarpour F, Karimipoor M, Arab A, Rajabi A, *et al.* Association between ABCB1-T1236C polymorphism and drug-resistant epilepsy in Iranian female patients. Iran Biomed J 2010;14:89-96.
49. Lakhan R, Misra UK, Kalita J, Pradhan S, Gogtay NJ, Singh MK, *et al.* No association of ABCB1 polymorphisms with drug-refractory epilepsy in a North Indian population. Epilepsy Behav 2009;14:78-82.
50. Lakhan R, Kumari R, Singh K, Kalita J, Misra UK, Mittal B. Possible role of CYP2C9 & CYP2C19 single nucleotide polymorphisms in drug refractory epilepsy. Indian J Med Res 2011;134:295-301.
51. Kumari R, Lakhan R, Garg RK, Kalita J, Misra UK, Mittal B. Pharmacogenomic association study on the role of drug metabolizing, drug transporters and drug target gene polymorphisms in drug-resistant epilepsy in a North Indian population. Indian J Hum Genet 2011;17:S32-40.
52. Dutta S, Gangopadhyay PK, Sinha S, Chatterjee A, Ghosh S, Rajamma U. An association analysis of reelin gene (RELN) polymorphisms with childhood epilepsy in Eastern Indian population from West Bengal. Cell Mol Neurobiol 2011;31:45-56.
53. Ratnapriya R, Vijai J, Kadandale JS, Iyer RS, Radhakrishnan K, Anand A. A locus for juvenile myoclonic epilepsy maps to 2q33-q36. Hum Genet 2010;128:123-30.
54. Kapoor A, Vijai J, Ravishankar HM, Satishchandra P, Radhakrishnan K, Anand A. Absence of GABRA1 Ala322Asp mutation in juvenile myoclonic epilepsy families from India. J Genet 2003;82:17-21.
55. Kapoor A, Satishchandra P, Ratnapriya R, Reddy R, Kadandale J, Shankar SK, *et al.* An idiopathic epilepsy syndrome linked to 3q13.3-q21 and missense mutations in the extracellular calcium sensing receptor gene. Ann Neurol 2008;64:158-67.
56. Fong GC, Shah PU, Gee MN, Serratosa JM, Castroviejo IP, Khan S, *et al.* Childhood absence epilepsy with tonic-clonic seizures and electroencephalogram 3-4-Hz spike and multispike-slow wave complexes: Linkage to chromosome 8q24. Am J Hum Genet 1998;63:1117-29.
57. Mariani J, Simonini MV, Palejev D, Tomasini L, Coppola G, Szekely AM, *et al.* Modeling human cortical development *in vitro* using induced pluripotent stem cells. Proc Natl Acad Sci U S A 2012;109:12770-5.
58. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, *et al.* Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 2007;131:861-72.
59. Lancaster MA, Renner M, Martin CA, Wenzel D, Bicknell LS, Hurles ME, *et al.* Cerebral organoids model human brain development and microcephaly. Nature 2013;501:373-9.