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Genetic testing in the epilepsies —developments and dilemmas

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Abstract

In the past two decades, the number of genes recognized to have a role in the epilepsies has dramatically increased. The availability of testing for epilepsy-related genes is potentially helpful for clarification of the diagnosis and prognosis, selection of optimal treatments, and provision of information for family planning. For some patients, identification of a specific genetic cause of their epilepsy has important personal value, even in the absence of clear clinical utility. The availability of genetic testing also raises new issues that have only begun to be considered. These issues include the growing importance of educating physicians about when and how to test patients, the need to ensure that affected individuals and their families can make informed choices about testing and receive support after receiving the results, and the question of what the positive and negative consequences of genetic testing will be for affected individuals, their family members, and society.

Introduction

The availability of clinical genetic testing in the epilepsies has increased dramatically because of rapid progress in identifying the causative mutations (discussed in another article in this issue),[1] as well as advances in laboratory techniques.[2–8] In addition to traditional Sanger sequencing, which is used to identify mutations in individual genes linked to epilepsy and related disorders, clinicians are now presented with an expanded repertoire of testing modalities (Table 1). Chromosomal microarray analysis (CMA) is now often the first genetic evaluation conducted in patients with epilepsy and provides information about chromosomal aneuploidies previously detected by high-resolution karyotyping, as well as about smaller deletions and duplications.

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Epilepsy-specific gene panels have become available to test for sequence variants and whole or partial gene deletions and duplications in multiple genes. Currently available panels can simultaneously screen many potentially relevant genes, and do not require the same degree of pretest correlation of genotype to phenotype as is needed for selection of a single-gene test. These panels also have the advantage of being able to detect intragenic deletions that are below the resolution of CMA and might also be missed by Sanger sequencing (heterozygous deletion of one or more exons of a gene cannot be detected using the Sanger method, because the remaining normal copy of those exons provides a normal sequencing result).

Whole-exome sequencing (WES) is also clinically available, and can provide information about putative pathogenic variants—not only in genes already known to be related to a specific epilepsy syndrome, but also in genes that might not be expected to harbour mutations, particularly if the epilepsy phenotype differs from that previously observed to be associated with the variant in question.[9–11] When applied to a trio (the patient and both biological parents), WES provides an efficient approach to the discovery of both *de novo* and inherited mutations in the coding portions of most genes in the human genome. Whole-genome sequencing (WGS), which is widely performed in the research setting, will probably also shortly be available in the clinic and will provide a means to assay both point mutations and copy number variations across the whole genome.[12]

In this article, we discuss these developments and focus on new issues that they bring to light, particularly those related to the benefits and risks of testing and challenges for the provision of genetic services (Box 1). Genetic testing in the epilepsies has the potential to revolutionize the care of affected patients, but to ensure services are delivered in the most effective, sensitive, and equitable manner possible, we need to devote attention to the challenges involved and establish mechanisms to address them.

Box 1

Questions raised by the advent of genetic testing in the epilepsies

Informed choice

- What approaches are needed to empower individuals to make an informed choice about whether or not to be tested?

Interpreting results

- What approaches are needed to help patients and family members comprehend and cope with the results?

Impact

- What are the positive and negative, short-term and long-term effects on an affected individual of receiving a genetic diagnosis?
- Will unaffected family members choose to learn their genetic status and, if so, how will this influence their lives?

- How does the impact of testing relate to specific clinical features of epilepsy (such as childhood versus adult onset, severity and associated intellectual disability)?

Incidental findings

- What should be done to deal with the possibility that genetic findings unrelated to epilepsy will be discovered?

Cost

- What systems should be used to cover the costs of potentially expensive new technologies?
- How can we ensure equity in access to new genetic testing technologies?

Data storage

- What systems can be developed for storage and management of the massive volume of data from whole-exome and whole-genome sequencing?

Changes over time

- How can advances in the available tests and in the interpretation of results be managed, especially if informative results are not obtained on initial testing?

Geneticization

- What will be the effect on public views of epilepsy of the perception that it is a genetic disorder?

Medical education

- What approaches should be used to ensure that treating clinicians are equipped to recognize when testing should be offered, which tests are most likely to be useful in specific situations, and how to order tests?
- How can we expand the workforce of genetic counsellors equipped to advise patients and families with epilepsy?

Challenges for interpretation

Each genetic testing modality brings challenges related to the interpretation of molecular findings in a clinical context. A clearly positive result can provide a definitive explanation of the patient's epilepsy. A negative result must be considered within the limits and complexities of the technology and data interpretation, and does not rule out a genetic cause of epilepsy in the individual tested.

When interpreting the results of a CMA, in terms of considering the potential pathogenicity of a deletion or duplication, factors such as the location, size, gene(s) affected, and any relevant association with disease corresponding to the individual's phenotype are all very important. For example, in a patient with early-onset epilepsy, intellectual disability and dysmorphic features, the finding of a deletion or duplication that has previously been reported as pathogenic and has been associated with these phenotypic features would be

considered a positive result. A negative CMA result tells us that a patient does not have a detectable deletion or duplication, although it is important to keep in mind that this detection technique is becoming more sensitive over time as the technology advances. Often, however, individuals have CMA findings that are of undetermined significance because the detected anomaly has not previously been associated with disease nor specifically classified as benign in databases such as the Database of Genomic Variants.[13] Such findings might need to be interpreted in the context of parental genetic test results. If an unaffected parent carries the same deletion or duplication as a patient with an epilepsy phenotype, the variant is usually judged to be benign, but clinicians must also acknowledge the possibility that the variant has incomplete penetrance.

For single-gene or multiple-gene (panel) testing, variants in a given gene must be considered carefully in the context of previously reported mutations, type of variant, and frequency in the 'background' population (whose sequence data are compiled in a growing number of publicly available databases, detailed below). Generally, laboratories will report variants to be pathogenic if they have been associated in the literature with the phenotype in question; however, the strength of the published evidence in favour of pathogenicity varies from *in silico* predictions of pathogenicity to functional characterization of the mutation in *in vitro* or even *in vivo* models. For a previously unreported variant, the type of variant may aid assessment of its potential pathogenicity. For example, a nonsense variant that results in a premature stop codon and protein truncation is more likely to be pathogenic than is a missense variant resulting in a single amino acid substitution. In the absence of specific functional studies, however, prediction of the effects of a given variant relies on knowledge of the structure of the gene's protein product and its critical domains, and (for missense variants) conservation across species of the specific amino acid in question.

New methods to assess a gene's tolerance of variation have been described in the research setting,[9,14] and several tools to predict the functional effects of variants, such as Polyphen-2[15] and SIFT,[16] are available to laboratories and clinicians. In addition, publicly available databases such as the 1,000 Genomes Project[17] and the National Heart Lung and Blood Institute Exome Variant Server[18] enable laboratories to evaluate whether a newly identified variant in a patient with epilepsy has also been seen in populations of individuals who are not known to have diseases. However, since epilepsy is not a rare disease and the clinical presentation can vary among individuals with the same mutation, even within a family, the finding that a given variant is present at low frequency in these databases does not completely rule out pathogenicity. As with CMA, interpretation of the potential pathogenicity of a variant identified in single-gene and gene-panel testing might require testing of the biological parents of an affected individual.

As WES (and eventually WGS) become more widely used, the same issues will apply. The current practice of applying WES and WGS to a trio, although costly at the outset, provides tremendous efficiency in the analysis of *de novo* variants. These whole-genome approaches will also lead to the identification of many additional variants of unknown significance in patients with epilepsy and the possible identification of novel epilepsy-related genes. The need for iterative re-evaluation of genetic findings, especially variants of uncertain significance, is increasingly recognized in the face of this growing body of publicly

available data. Laboratories that currently perform clinical genetic testing for epilepsy are generally willing to re-evaluate the potential pathogenicity of variants, but this step is currently done on an *ad hoc* basis and only at the request of treating clinicians. To facilitate the interpretation and reinterpretation of genetic data, the epilepsy genetics community might benefit from the creation of a centralized database of pathogenic mutations and variants of uncertain significance.

Potential benefits and risks

Several factors need to be considered in evaluating the potential value of a genetic test (Box 2). For several epilepsy-related genes, diagnostic testing has clear implications for treatment or prognosis (Table 2). In individuals suspected to have Dravet syndrome, for example, detection of a pathogenic mutation in *SCN1A* hastens diagnosis, thereby reducing uncertainty for patients and their families and avoiding expensive, uncomfortable or invasive tests (such as repeated imaging, video electroencephalography, muscle biopsy, and lumbar puncture), as well as possibly inappropriate treatment.[4,5,19] A patient might turn out to have a pathogenic mutation in a gene that was not initially suspected on the basis of his or her initial presenting phenotype—for example, a mutation that causes a metabolic disease—and the genetic diagnosis could lead to gene-specific treatment, such as pyridoxine therapy for pyridoxine-dependent epilepsy.

Box 2

The value of genetic testing

In epilepsy, as in other disorders, the potential value of a genetic test depends on the following four factors:[4]

Analytic validity

Accuracy in detecting an epilepsy-related genotype

Clinical validity

Accuracy in predicting a clinical phenotype, determined by both positive predictive value (the degree to which a positive result predicts a given syndrome) and negative predictive value (the degree to which a negative result rules out a syndrome)

Clinical utility

Whether the test results have implications for the patient's clinical care

Personal utility

The value of the test results for the patient, independent of any implications for clinical care

Even in the absence of implications for treatment, a genetic diagnosis can alert the clinician and patient to screen for other symptoms that are associated with the gene mutation. Importantly, the test results can provide answers to questions about what did or did not cause the disorder, which can bring relief or comfort to patients and caregivers, and might

also facilitate procurement of support from other affected individuals or families. A genetic diagnosis can also help with reproductive decisions and, for some families (especially those affected by severe epilepsies associated with developmental disability), could provide possibilities for prenatal or preimplantation genetic diagnosis in future pregnancies.

New test modalities have an increased yield of molecular diagnosis, particularly in patients with severe, early-onset epilepsies. For example, in one study, targeted resequencing of 265 candidate genes identified mutations that were presumed to be disease-causing in 16 of 33 patients, many of whom had severe epilepsies associated with intellectual disability.[20] Pathogenic mutations were identified in 10% of patients with infantile epileptic encephalopathies through targeted resequencing of 65 genes[21] and, in approximately 15% of such patients, through WES.[9,22] However, most epilepsy syndromes are genetically heterogeneous; mutations in different genes cause the same syndrome in different individuals or families, and only a fraction of the potential genetic causes have so far been identified. Consequently, although a positive test result can confirm or suggest that an individual has a specific syndrome, a negative test result might be uninformative. For instance, fewer than 1 in five individuals with autosomal dominant nocturnal frontal lobe epilepsy have a mutation in any of the genes currently associated with that disorder;[4,8] thus, a negative genetic test result does not preclude the clinical diagnosis. Similarly, although use of advanced testing modalities increases the yield of mutation detection substantially, a negative test with these approaches is also uninformative.

Conversely, in syndromes with incomplete penetrance and variable expressivity, a positive test result in an unaffected family member does not necessarily mean that she will develop epilepsy in the future, nor can it predict the specific phenotype if she does. An important example of this problem is genetic epilepsy with febrile seizures plus (GEFS+), in which some family members with a *SCN1A* mutation remain unaffected, and phenotypes in affected family members vary from simple age-limited febrile seizures to severe epileptic encephalopathies.[4,5]

The risk of epilepsy is increased approximately threefold in first-degree relatives of individuals with epilepsy,[23] and twin studies consistently confirm a genetic component to this increased familial risk.[24–27] Most people with epilepsy, however, have no affected relatives. For example, in a population-based study conducted by our research group, only around 15% of probands with incident epilepsy had one or more first-degree relative with epilepsy.[23] Most individuals with a family history had just one affected relative, and in very few families did the history seem consistent with a Mendelian model of inheritance.

As with many common disorders, inheritance in the majority of individuals with epilepsy is likely to be complex and multi-factorial, with most of the genetic influence contributed by variants that individually have a small or modest effect, and act in concert with each other and with (as yet unspecified) environmental factors. In forms of epilepsy with complex inheritance, genetic testing might need to involve analysis of combinations of risk-raising alleles in multiple genes, rather than looking for a causative mutation in a single gene.[28] This approach, which has yet to be developed, would offer considerable potential, particularly if it could enable the identification of patient subgroups with different

implications for treatment or prognosis. Beyond the implications of having a genetic diagnosis for an individual patient, the ability to define cohorts of patients according to genotype could also enable the development of targeted and genotype-specific clinical trials.

The potential clinical and personal utility of genetic testing differs according to whether it is a diagnostic test conducted in individuals who are already known or suspected to have epilepsy or a predictive test performed in individuals at risk. Whereas many individuals with epilepsy (or their caregivers) are strongly motivated to find the reason why they developed the disorder, how many of their unaffected (but at-risk) relatives would choose to be tested, and what the positive and negative effects of such testing will be, are less clear. A negative test result clearly can relieve anxiety and reduce the need for vigilance about possible seizure onset. However, a positive test result might also afford benefits, such as enabling individuals to prepare for possible seizure onset by alerting their families and physicians, and taking precautions to prevent accidents.[29]

Both diagnostic and predictive genetic testing carry potential risks. Although having a genetic explanation for their epilepsy is comforting for many individuals, research in other disorders suggests that some affected individuals might have less favourable reactions.[30,31] A positive test result in unaffected relatives, who then face the possibility of future seizure onset, might impair quality of life. Discrimination against these individuals in health insurance, life insurance, or employment—or fear thereof—is another possible adverse outcome.[32,33] In the USA, the Genetic Information Nondiscrimination Act (GINA), enacted in 2008, provides protection against discrimination in health insurance but no protection in disability insurance, long-term care insurance or life insurance. In addition, GINA does not cover military personnel, certain categories of veterans, or individuals cared for by the Indian Health Service.[34]

Few studies have specifically addressed genetic testing from the perspective of people with epilepsy.[19,29,35,36] In a qualitative study of risk perception and the perceived effects of genetic testing among research participants,[29] most individuals said they would want genetic testing if it were offered. They cited many potential advantages, including learning what caused epilepsy, being able to make informed reproductive choices, reducing guilt, relieving anxiety, and having an improved ability to care and advocate for children at risk. They also expressed concern about potential negative effects of genetic testing, including external pressure to modify their reproductive choices, increased blame and guilt, increased stigma, discrimination in employment and insurance, self-imposed limitations on life goals, and alterations in public conceptions of epilepsy.

Stigma is an important issue that pervades the experience of having epilepsy.[37–42] The influence of genetic testing on either perceived or actual experiences of stigma or discrimination has not been studied, but research in other stigmatized conditions provides cause for concern about the consequences of genetic attributions for epilepsy,[43,44] including the possibility that biological relatives of people with epilepsy might also experience discrimination[44] and ‘associative’[45] or ‘courtesy’ stigma.[46] Additionally, people with epilepsy and their family members have suggested that the increasing perception of epilepsy as a genetic disorder might change the way that the condition is perceived by society at

large, with potential positive and negative consequences for people with epilepsy as well as their family members.[29]

Provision of genetic services

Challenges for clinicians

The landscape of genetic testing for epilepsy is challenging to navigate for many clinicians, which heightens the importance of developing clear guidelines and improving medical education in genetics for clinicians working in the field of epilepsy. In addition to understanding the phenotypes in which testing is likely to be useful, and the types of tests available, clinicians must also be familiar with how to conduct clinical genetic testing, including the need for pretest and post-test genetic counselling, and possibly testing of family members in addition to the patient.

Owing to the extreme clinical and genetic heterogeneity of the epilepsies and the rapid pace of genetic discovery, decisions about which test(s) to perform can be complex. Careful phenotyping—including seizure types, age at onset, EEG patterns, and associated comorbidities (such as dysmorphic features, intellectual disability, or a movement disorder)—can suggest a syndrome associated with variants in a specific gene or set of genes. Targeted testing of an individual gene or small set of genes (including both sequencing and testing for deletions and duplications within the gene) is likely to be the most appropriate option for such patients. Similarly, CMA should be performed if a large-scale deletion or duplication syndrome is suspected. If the phenotype does not suggest a particular molecular diagnosis, use of CMA or a panel that includes sequencing and deletion or duplication testing for several epilepsy-associated genes might be indicated. This semi-targeted approach has the advantage of detecting copy number abnormalities as well as comprehensively assessing known epilepsy-related genes. When these modalities fail to result in a clear genetic diagnosis, WES might be indicated.

Another impediment to the provision of genetic testing services is the time (and associated costs) involved. Some physicians are dissuaded from genetic testing because of the time required for the consent process, obtaining and completing sometimes cumbersome order forms, follow-up of results (including variants of uncertain significance, which could in the future be reclassified as either benign or pathogenic, necessitating a system for recontacting patients) and, sometimes, arranging testing of parents or other relatives. As genetic testing continues to be expensive and is not always covered by insurance, physicians also confront the possibility of adding to the patient's financial burden in exchange for knowledge that may not change their clinical management or outcome.

To ensure competence in genetics among physicians in the USA,[47–49] guidelines have been developed by the National Coalition for Health Professional Education in Genetics.[50] In addition, a working group convened by the NIH, Centers for Disease Control and Prevention, and Health Resources and Services Administration, developed a list of specific genetic knowledge domains for maternal and child health primary care providers.[51] A similar set of guidelines should be developed for neurologists caring for patients with epilepsy, particularly in light of the results of a survey of neurologists and psychiatrists in

the USA, in which only about one-third of respondents said they were confident about how to order genetic tests.[52,53] In the same survey, fewer than half of participating neurologists reported they had access to a geneticist or genetic counsellor to whom they could refer patients.[53] Few genetic counsellors are familiar with the clinical and genetic aspects of the epilepsies, and additional training of counsellors is also needed to expand the available work-force and ensure access to counselling for disadvantaged populations.

Challenges for patients

Not surprisingly, the concepts surrounding genetic diagnosis, epilepsy inheritance and molecular testing are also challenging for many patients and their families. Many individuals expect that molecular testing will yield a diagnosis, specific prognostic information, and a specific treatment. In addition, testing may often take place during highly stressful medical situations, such as hospitalization for intractable seizures, in the setting of chronic, recurrent or episodic illness that has significantly affected quality of life. Testing of presymptomatic at-risk relatives is also a time of high anxiety. Moreover, when comprehensive testing approaches are used, positive results might be found in genes that are not expected to be responsible for the patient's epilepsy symptoms, as well as incidental (or secondary) positive findings in genes of relevance to other disorders. In March 2013, the American College of Medical Genetics and Genomics recommended that when WES or WGS is performed for clinical genetic testing, incidental results should be disclosed to patients in relation to 57 genes with actionable findings.[54] This recommendation raised considerable controversy, primarily focused on patients' right to refuse such information and the ethics of disclosing information about adult disorders in children.[55–58]

Cultural, familial and individual variations in understanding of epilepsy,[59–62] heritability[63] and risk[64] also need to be addressed. People in families affected by epilepsy may have 'personal theories of inheritance' based on their perceptions of shared physical or personality traits among family members.[29,65] Clinicians' failure to be aware of these factors can lead to miscommunication, conflict and adverse outcomes for people with epilepsy. Consequently, clinicians need to be prepared both to explain epilepsy, genetic risk and heritability from a biomedical perspective, and to respond sensitively to the ways in which people with epilepsy and their family members understand these concepts.

Finally, genetic testing may not be available for all segments of the population, particularly because its cost is not always covered by insurance. Though the costs of sequencing are falling rapidly, complex issues persist in relation to laboratory charges, institutional billing and insurance coverage that present barriers to clinical genetic testing for some patients. Advocacy might be needed to ensure equity in availability of genetic testing, particularly in situations where clinical utility is potentially high, as well as in access to treatment following testing.

Genetic counselling

For all the reasons described above, genetic counselling is essential to ensure that affected individuals and family members considering genetic testing for epilepsy are able to make an informed choice. The focus of genetic counselling might differ depending on whether it

involves a teenager or adult with epilepsy, the parents of a young child with epilepsy, or an at-risk family member. The approach to counselling should, therefore, be tailored to the individual, but several crucial elements should always be included.

Pretest genetic counselling should include a discussion of the risks, benefits and limitations of the particular type of test being considered. It is important to emphasize, in realistic terms, the likelihood of a positive test result and the potential influence (often limited or even negligible) that a genetic diagnosis could have on treatment and outcome. Patients (or their parents) need to be aware of the possibility that variants of uncertain significance could be found, and the potential need for follow-up testing of parents or other family members. Further, it is important that parents understand that genetic testing of young children could reveal epilepsy-related diagnoses that otherwise might not have become apparent for a substantial period of time (such as Lafora progressive myoclonic epilepsy). In relation to WES or WGS, the family should also be informed about the possibility of incidental findings unrelated to epilepsy (such as a *BRCA1* mutation). Finally, the pretest counselling session should involve a discussion of the expected turnaround time for obtaining test results, as well as the cost of testing and possible insurance coverage.

Post-test genetic counselling is equally important. Ideally the return of test results should take place during a scheduled, in-person follow-up visit specifically for this purpose. Given that test results might not be available until several months after the initial (pretest) counselling session, patients and their families might not remember the details. Importantly, patients and their family members might not be emotionally prepared to receive genetic test results and could experience unanticipated reactions to receiving a diagnosis. The parents of very young infants with epilepsy might be extremely distressed to learn that their child has an untreatable genetic condition, some of which are associated with severe intellectual or motor disability. Even parents with a severely disabled child, for whom they have actively sought a genetic diagnosis for many years, could be caught off guard and feel unexpected guilt at having passed on a gene mutation. Individuals living with epilepsy who themselves have sought a genetic explanation could find relief in a genetic diagnosis, but might worry about how to communicate the information to other family members, especially those who might also be at risk. Asymptomatic but at-risk family members undergoing predictive testing might experience extreme distress on receiving positive test results, but even family members who test negative for the gene mutation can feel traumatized and experience survivor guilt, as observed in other disorders.[66] Genetic counsellors must, therefore, be prepared to address the guilt, shame and blame that can accompany the receipt of a genetic diagnosis, to provide written resources and information about support organizations that may facilitate contact with other affected families, and to refer individuals to mental health professionals if needed.

The implications of a genetic diagnosis for reproductive decisions are an extremely important concern for people with epilepsy, and criteria are urgently needed for genetic counselling in this context. Evidence suggests that many individuals with epilepsy greatly overestimate the risks of epilepsy in their offspring, and many limit childbearing because of concerns about genetic risk.[35] The potential harms and benefits of genetic information in this context are a major concern of people in multiplex families.[29]

Future research needs

Research into the genetics of epilepsy is moving very rapidly, and guidelines for the inclusion of new research findings in clinical testing protocols are urgently needed, based on validity of the findings, their clinical relevance, and their clinical and personal utility for affected individuals. The disclosure of results to participants in epilepsy genetics research might also be considered, and guidelines are needed for these circumstances as well. The development of clinical guidelines should be informed by empirical research involving the intended users of genetic testing—that is, people with epilepsy and their immediate family members, as well as clinicians.

As we have argued previously,[67] research on the ways in which genetic information might alter the experience of living with epilepsy is urgently needed because of the important psychosocial dimensions, which include stigma, discrimination, reduced rates of marriage and reproduction, and reduced quality of life.[38,42,68–74] We would especially encourage research to address optimal ways to educate clinical care providers in epilepsy genetics, the degree to which affected individuals understand the risks and benefits of genetic testing, optimal ways of enabling such individuals to make informed choices, and the positive and negative psychosocial effects on patients and family members of receiving genetic test results. The impact of genetic information is likely to be influenced by many factors, including the clinical context of epilepsy within a family (severity, age at onset, available treatments), individual characteristics (sex, life stage, ethnicity, education), and community context and values (religion, social networks, support, personal preferences).

The future holds promise for the development of new genetic testing approaches that translate into improved care for people with epilepsy, and even methods to prevent the onset of seizures in some at-risk individuals. With education and research, we should prepare ourselves for these exciting opportunities, so they can be provided in an optimal manner.

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References

1. Thomas, RH.; Berkovic, SF. The hidden genetics of epilepsy—a clinically important new paradigm. Nat Rev Neurol. http://dx.doi.org/10.1038/nrneurol.2014.62
2. Pal DK, Pong AW, Chung WK. Genetic evaluation and counseling for epilepsy. Nat Rev Neurol. 2010; 6:445–453. [PubMed: 20647993]
3. Pong AW, Pal DK, Chung WK. Developments in molecular genetic diagnostics: an update for the pediatric epilepsy specialist. Pediatr Neurol. 2011; 44:317–327. [PubMed: 21481738]
4. Ottman R, et al. Genetic testing in the epilepsies—report of the ILAE Genetics Commission. Epilepsia. 2010; 51:655–670. [PubMed: 20100225]
5. Hirose S, et al. *SCN1A* testing for epilepsy: application in clinical practice. Epilepsia. 2013; 54:946–952. [PubMed: 23586701]
6. Sheidley BR, Poduri A. Genetics in clinical epilepsy: issues in genetic testing and counseling. J Pediatr Epilepsy. 2012; 1:135–142.

7. Hildebrand MS, et al. Recent advances in the molecular genetics of epilepsy. J Med Genet. 2013; 50:271–279. [PubMed: 23468209]
8. Scheffer IE. Genetic testing in epilepsy: what should you be doing? Epilepsy Curr. 2011; 11:107–111. [PubMed: 21836823]
9. Epi4K Consortium & Epilepsy Phenome/ Genome Project. *De novo* mutations in epileptic encephalopathies. Nature. 2013; 501:217–221. [PubMed: 23934111]
10. Yu TW, et al. Using whole-exome sequencing to identify inherited causes of autism. Neuron. 2013; 77:259–273. [PubMed: 23352163]
11. Alkuraya FS. The application of next-generation sequencing in the autozygosity mapping of human recessive diseases. Hum Genet. 2013; 132:1197–1211. [PubMed: 23907654]
12. Martin, HC., et al. Clinical whole-genome sequencing in severe early onset epilepsy reveals new genes and improves molecular diagnosis. Hum Mol Genet. http://dx.doi.org/10.1093/hmg/ddu030
13. Database of Genomic Variants. 2014. [online], http://dgv.tcag.ca/dgv/app/home
14. Petrovski S, Wang Q, Heinzen EL, Allen AS, Goldstein DB. Genic intolerance to functional variation and the interpretation of personal genomes. PLoS Genet. 2013; 9:e1003709. [PubMed: 23990802]
15. PolyPhen-2: prediction of functional effects of human nsSNPs. 2014. [online], http://genetics.bwh.harvard.edu/pph2/
16. J. Craig Venter Institute. SIFT. 2014. [online], http://sift.jcvi.org/
17. The 1,000 Genomes Project: a deep catalog of human genetic variation. 2014. [online], www.1000genomes.org
18. National Heart Lung Blood Institute (NHLBI). Exome Sequencing Project (ESP) Exome Variant erver (EVS). 2014. [online] http://evs.gs.washington.edu/EVS
19. Brunklaus A, et al. The clinical utility of an *SCN1A* genetic diagnosis in infantile-onset epilepsy. Dev Med Child Neurol. 2013; 55:154–161. [PubMed: 23163885]
20. Lemke JR, et al. Targeted next generation sequencing as a diagnostic tool in epileptic disorders. Epilepsia. 2012; 53:1387–1398. [PubMed: 22612257]
21. Carvill GL, et al. Targeted resequencing in epileptic encephalopathies identifies *de novo* mutations in *CHD2* and *SYNGAP1*. Nat Genet. 2013; 45:825–830. [PubMed: 23708187]
22. Veeramah KR, et al. Exome sequencing reveals new causal mutations in children with epileptic encephalopathies. Epilepsia. 2013; 54:1270–1281. [PubMed: 23647072]
23. Peljto AL, et al. Familial risk of epilepsy: a population-based study. Brain. 2014; 137:795–805. [PubMed: 24468822]
24. Vadlamudi L, et al. Epilepsy in twins: insights from unique historical data of William Lennox. Neurology. 2004; 62:1127–1133. [PubMed: 15079012]
25. Berkovic SF, Howell RA, Hay DA, Hopper JL. Epilepsies in twins: genetics of the major epilepsy syndromes. Ann Neurol. 1998; 43:435–445. [PubMed: 9546323]
26. Corey LA, et al. The occurrence of epilepsy and febrile seizures in Virginian and Norwegian twins. Neurology. 1991; 41:1433–1436. [PubMed: 1891093]
27. Kjeldsen MJ, Corey LA, Christensen K, Friis ML. Epileptic seizures and syndromes in twins: the importance of genetic factors. Epilepsy Res. 2003; 55:137–146. [PubMed: 12948623]
28. Klassen T, et al. Exome sequencing of ion channel genes reveals complex profiles confounding personal risk assessment in epilepsy. Cell. 2011; 145:1036–1048. [PubMed: 21703448]
29. Shostak S, Zarhin D, Ottman R. What's at stake? Genetic information from the perspective of people with epilepsy and their family members. Soc Sci Med. 2011; 73:645–654. [PubMed: 21831495]
30. Lehmann A, Speight BS, Kerzin-Storrar L. Extended family impact of genetic testing: the experiences of X-linked carrier grandmothers. J Genet Couns. 2011; 20:365–373. [PubMed: 21491179]
31. Douglas HA, Hamilton RJ, Grubs RE. The effect of *BRCA* gene testing on family relationships: a thematic analysis of qualitative interviews. J Genet Couns. 2009; 18:418–435. [PubMed: 19479365]

32. Burke W, Pinsky LE, Press NA. Categorizing genetic tests to identify their ethical, legal, and social implications. Am J Med Genet. 2001; 106:233–240. [PubMed: 11778984]
33. Jacoby K, Jacoby A. Epilepsy and insurance in the UK: an exploratory survey of the experiences of people with epilepsy. Epilepsy Behav. 2004; 5:884–893. [PubMed: 15582837]
34. Baruch S, Hudson K. Civilian and military genetics: nondiscrimination policy in a post-GINA world. Am J Hum Genet. 2008; 83:435–444. [PubMed: 18940308]
35. Helbig KL, et al. Genetic risk perception and reproductive decision making among people with epilepsy. Epilepsia. 2010; 51:1874–1877. [PubMed: 20163441]
36. Hammond CL, Thomas RH, Rees MI, Kerr MP, Rapport F. Implications for families of advances in understanding the genetic basis of epilepsy. Seizure. 2010; 19:675–679. [PubMed: 21095138]
37. Gehlert S, DiFrancesco A, Chang CH. Black–white differences in the psychosocial outcomes of epilepsy. Epilepsy Res. 2000; 42:63–73. [PubMed: 10996507]
38. Jacoby A. Stigma, epilepsy, and quality of life. Epilepsy Behav. 2002; 3:S10–S20.
39. Jacoby A, Gorry J, Gamble C, Baker GA. Public knowledge, private grief: a study of public attitudes to epilepsy in the United Kingdom and implications for stigma. Epilepsia. 2004; 45:1405–1415. [PubMed: 15509242]
40. Morrell M. Stigma and epilepsy. Epilepsy Behav. 2002; 3:S21–S25.
41. Scambler G. Health-related stigma. Sociol Health Illn. 2009; 31:441–455. [PubMed: 19366430]
42. Schneider, JW.; Conrad, P. Having Epilepsy: the Experience and Control of Illness. Temple University Press; 1983.
43. Bennett L, Thirlaway K, Murray AJ. The stigmatising implications of presenting schizophrenia as a genetic disease. J Genet Couns. 2008; 17:550–559. [PubMed: 18773286]
44. Phelan JC. Geneticization of deviant behavior and consequences for stigma: the case of mental illness. J Health Soc Behav. 2005; 46:307–322. [PubMed: 16433278]
45. Mehta SI, Farina A. Associative stigma: perceptions of the difficulties of college-aged children of stigmatized fathers. J Social Clin Psychol. 1988; 7:192–202.
46. Goffman, E. Stigma: Notes on the Management of Spoiled Identity. Prentice Hall; 1963.
47. Feero WG. Genetics of common disease: a primary care priority aligned with a teachable moment? Genet Med. 2008; 10:81–82. [PubMed: 18281913]
48. Burke W, Emery J. Genetics education for primary-care providers. Nat Rev Genet. 2002; 3:561–566. [PubMed: 12094234]
49. Feero WG, Green ED. Genomics education for health care professionals in the 21st century. JAMA. 2011; 306:989–990. [PubMed: 21900139]
50. Core Competency Working Group of the National Coalition for Health Professional Education in Genetics. Recommendations of core competencies in genetics essential for all health professionals. Genet Med. 2001; 3:155–159. [PubMed: 11280953]
51. Kemper AR, et al. A blueprint for maternal and child health primary care physician education in medical genetics and genomic medicine: recommendations of the United States Secretary for Health and Human Services Advisory Committee on heritable disorders in newborns and children. Genet Med. 2010; 12:77–80. [PubMed: 20084011]
52. Kang PB. Ethical issues in neurogenetic disorders. Handb Clin Neurol. 2013; 118:265–276. [PubMed: 24182384]
53. Salm M, et al. Use of genetic tests among neurologists and psychiatrists: knowledge, attitudes, behaviors, and needs for training. J Genet Couns. 2014; 23:156–163. [PubMed: 23793969]
54. Green RC, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med. 2013; 15:565–574. [PubMed: 23788249]
55. Burke W, et al. Recommendations for returning genomic incidental findings? We need to talk! Genet Med. 2013; 15:854–859. [PubMed: 23907645]
56. Holtzman NA. ACMG recommendations on incidental findings are flawed scientifically and ethically. Genet Med. 2013; 15:750–751. [PubMed: 24008255]
57. McGuire AL, et al. Point–counterpoint. Ethics and genomic incidental findings. Science. 2013; 340:1047–1048. [PubMed: 23686340]

58. Wolf SM, Annas GJ, Elias S. Point–counterpoint. Patient autonomy and incidental findings in clinical genomics. Science. 2013; 340:1049–1050. [PubMed: 23686341]
59. Ghanean H, Nojomi M, Jacobsson L. Public awareness and attitudes towards epilepsy in Tehran, Iran. Glob Health Action. 2013; 6:21618. [PubMed: 24314322]
60. Keikelame MJ, Swartz L. A lay carer's story about epilepsy in an urban South African context: they call it an illness of falling or an illness of fitting because a person shakes and eventually falls. Epilepsy Behav. 2013; 28:512–518. [PubMed: 23838162]
61. Good BJ, Del Vecchio Good MJ. In the subjunctive mode: epilepsy narratives in Turkey. Soc Sci Med. 1994; 38:835–842. [PubMed: 8184334]
62. Fadiman, A. The Spirit Catches You and You Fall Down: a Hmong Child, her American Doctors, and the Collision of Two Cultures. Farrar Straus and Giroux; 1997.
63. Whitmarsh, I. Biomedical Ambiguity: Race, Asthma, and the Contested Meaning of Genetic Research in the Caribbean. Cornell University Press; 2008.
64. Rapp, R. Testing Women, Testing the Fetus: the Social Impact of Amniocentesis in America. Routledge; 1999.
65. McAllister M. Personal theories of inheritance, coping strategies, risk perception and engagement in hereditary non-polyposis colon cancer families offered genetic testing. Clin Genet. 2003; 64:179–189. [PubMed: 12919131]
66. d'Agincourt-Canning L. A gift or a yoke? Women's and men's responses to genetic risk information from *BRCA1* and *BRCA2* testing. Clin Genet. 2006; 70:462–472. [PubMed: 17100990]
67. Shostak S, Ottman R. Ethical, legal, and social dimensions of epilepsy genetics. Epilepsia. 2006; 47:1595–1602. [PubMed: 17054679]
68. Taylor J, Baker GA, Jacoby A. Levels of epilepsy stigma in an incident population and associated factors. Epilepsy Behav. 2011; 21:255–260. [PubMed: 21576039]
69. Leaffer EB, et al. Associates of stigma in an incident epilepsy population from northern Manhattan, New York City. Epilepsy Behav. 2011; 21:60–64. [PubMed: 21482485]
70. Fernandes PT, Snape DA, Beran RG, Jacoby A. Epilepsy stigma: what do we know and where next? Epilepsy Behav. 2011; 22:55–62. [PubMed: 21458385]
71. Austin JK, et al. Self-esteem and symptoms of depression in children with seizures: relationships with neuropsychological functioning and family variables over time. Epilepsia. 2010; 51:2074–2083. [PubMed: 20412284]
72. Hermann B, Jacoby A. The psychosocial impact of epilepsy in adults. Epilepsy Behav. 2009; 15 (Suppl 1):S11–S16. [PubMed: 19318133]
73. Jacoby A. Epilepsy and stigma: an update and critical review. Curr Neurol Neurosci Rep. 2008; 8:339–344. [PubMed: 18590619]
74. Scambler G. Patient perceptions of epilepsy and of doctors who manage epilepsy. Seizure. 1994; 3:287–293. [PubMed: 7894839]

Table 1

Clinically available genetic testing modalities in epilepsy

Test	Scope	Indication	Advantages	Disadvantages
CMA	Targeted and untargeted (includes known disease loci as well as a survey across the chromosomes)	Unexplained epilepsy, especially with intellectual disability and/or autism Suspected chromosomal microdeletion or duplication syndrome	Simultaneous targeted and untargeted approach May provide information about regions of homozygosity in consanguineous individuals, thereby possibly suggesting specific genes Relatively fast (few weeks)	Rarely, can miss a chromosomal rearrangement such as a ring chromosome abnormality, but high-resolution clinical CMA typically detects small deletions at the site of rearrangements
Karyotyping	Untargeted	Suspected monosomy, trisomy or chromosomal rearrangement; maternal history of recurrent pregnancy losses; generally recommended if strong suspicion and CMA result is negative	Fast (few days)	Lower resolution than CMA
Single-gene testing	Targeted	Syndromes usually associated with specific gene(s)	Faster and less expensive than gene-panel testing	Not all commercially available tests include deletion and duplication testing as well as sequencing
Gene-panel testing	Semi-targeted	Syndrome associated with several epilepsy-related genes, or syndrome not clearly related to specific gene	If several genes may be candidates for a syndrome, this option is more time-efficient than serial single-gene testing, and faster than WES and WGS	Not all commercially available tests include deletion and duplication testing, as well as sequencing Expensive
WES	Untargeted (but analysis should include targeted examination of specific genes of interest)	Epilepsy syndrome without specific gene associations	Currently, difficult to derive copy number information from WES data	Incidental findings Expensive Coverage of specific genes not guaranteed because of limitations in capture technology
WGS	Untargeted (but analysis should include targeted examination of specific genes or regions of interest)	Epilepsy syndrome without specific gene associations	Also enables evaluation for copy number abnormalities	Incidental findings Expensive Not yet covered by insurance

Abbreviations: CMA, chromosomal microarray analysis; WES, whole exome sequencing; WGS, whole genome sequencing.

Table 2

Epilepsy-related genetic variants with implications for clinical management

Gene variant	Syndrome(s)	Change in treatment	Other clinical implications
SCN1A	Dravet syndrome Migrating epilepsy of infancy	Avoidance or removal of some sodium channel agents (for example, phenytoin, lamotrigine) in some patients	Monitoring and management of progressive changes in gait Awareness of risk of sudden unexplained death in epilepsy
SLC2A1	Glucose transporter deficiency (GLUT1 syndrome)	Ketogenic diet should be tried	Monitoring for movement disorder
KCNQ2	Epileptic encephalopathy (also associated with a benign epilepsy syndrome)	Ezogabine specifically targets and modulates opening of the involved potassium channels, but its safety and efficacy in children has not been determined	None
PRRT2	Infantile convulsions (also associated with episodic ataxia, paroxysmal kinesigenic dyskinesia, and hemiplegic migraine)	Carbamazepine or oxcarbazepine might be effective	Surveillance for other neurological manifestations
TSC1 and *TSC2*	Tuberous sclerosis complex, often with infantile spasms	Vigabatrin might be effective Rapamycin and its derivatives might be effective (now in clinical trials)	Surveillance for tumours and non-neurological manifestations
ALDH7A1 and *PNPO*	Severe early-onset epilepsy	Pyridoxine should be used	None