A Genetic Panel With That Dilantin Level, Please?

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Introduction

The International League Against Epilepsy (ILAE) recently published a review of genetic testing in epilepsy.[1] Because of the increasing use of genetic testing in epilepsy and other disorders, physicians and other healthcare providers should be aware of advances in this field.

Genetic testing has 4 main functions: prenatal diagnosis, diagnosis, predictive testing, and carrier testing. Genetic testing may be carried out in research laboratories, ordered by clinicians, or obtained directly by the consumer, primarily through services marketed over the Internet. The ILAE report addresses both potential benefits and harms.

Genetic Abnormalities in Epilepsy

Epilepsy remains a clinical diagnosis, with no definitive diagnostic genetic, radiologic, electrophysiologic, or other test data. To date, more than 20 genes have been associated with genetic (idiopathic) epilepsies. In addition, seizures may be part of the clinical manifestations of other neurologic diseases, such as Tay-Sachs, for which genetic testing is available.

A variety of genetic epilepsy syndromes have been identified, such as those beginning in the first year of life, those with prominent febrile seizures, idiopathic generalized epilepsies, focal epilepsies, and epilepsies associated with other paroxysmal disorders. These may be associated with 1 or more abnormal gene products, which include sodium channels, potassium channels, gamma-aminobutyric acid-A receptors, calcium channels, aristaless-related homeobox protein, protocadherin, and others. The ILAE article provides a list of these, and more information is available on the publicly funded Gene Tests Website.

Techniques

Molecular methods for genetic testing include DNA sequencing, mutation scanning, targeted mutation analysis, fluorescent in situ hybridization, array-comparative genomic hybridization, single nucleotide polymorphism arrays, multiplex ligation-dependent probe amplification, and others.

Potential Benefits of Genetic Testing

To assist in the care of people with epilepsy, genetic testing may be helpful in 5 fundamental ways.

1. Confirm a suspected genetic syndrome. This may help the patient by limiting further diagnostic studies, which may be time-consuming, anxiety-producing, and expensive. Examples include Ohtahara syndrome, X-linked infantile spasms, autosomal dominant frontal lobe epilepsy, and epilepsy with paroxysmal exercise-induced dyskinesia, which may be confirmed with highly accurate genetic tests.

2. Direct therapy. At present, most genetic testing does not help the clinical neurologist control seizures in individual patients. However, 1 notable exception is severe myoclonic epilepsy in infancy (Dravet syndrome), an epileptic encephalopathy that presents with prolonged seizures in the first year of life. Dravet syndrome is characterized by status epilepticus, alternating

hemiconvulsions, myoclonic seizures, and developmental regression, and can be confused with Lennox-Gastaut syndrome, myoclonic-astatic epilepsy, benign myoclonic epilepsy, and other childhood epilepsies. Specific mutations of the voltage-gated sodium channel alpha subunit Na-v1.1 in the *SCNIA* gene are found in 67%-86% of children with Dravet syndrome [2] and can be identified with commercially available tests. Diagnosis is important because valproate, topiramate, and levetiracetam (and stiripentol in Europe) are more likely to control seizures, while carbamazepine and lamotrigine tend to aggravate them.[2] Early seizure control may improve long-term developmental outcome, highlighting the need for prompt, effective therapy.

3. Prenatal screening. Genetic testing has already had a definite impact in the incidence of neurologic diseases due to prenatal testing, and is becoming more accepted by physicians and the public. Thanks to the availability of prenatal genetic testing, inherited diseases such as familial dysautonomia may soon disappear.[3]

4. Advance research. The knowledge of genetic mutations underlying specific seizure disorders may guide the development of more effective therapies. For example, because the *SCNIA* gene mutation in Dravet syndrome affects the sodium channel, targeting therapies to overcome this defect may lead to innovative methods to control seizures. Increased understanding of genetic mutations underlying epileptic disorders may also lead to interventions that impede or stop epileptogenesis in patients at risk for the development of epilepsy due to inherited factors or acquired causes, such as head trauma or encephalitis.

5. Pharmacogenetic testing. Identifying genetic variations within individual patients may lead to the development of personalized medication therapy. Pharmacogenetic testing and treatment remain a largely unfulfilled promise of genetic testing. A related use is the identification of patients at risk from specific treatment. For example, testing for the HLA-B*1502 allele identifies patients more likely to develop a serious rash from carbamazepine.

Potential Harm of Genetic Testing

Psychological distress due to knowledge of a genetic defect, particularly one that leads to a disease without specific treatment, is a potential consequence of genetic testing. This drawback has been explored regarding other neurologic conditions such as Huntington's disease. People with known genetic disorders may perceive stigma related to their "bad genes." Needless to say, delivery of genetic information to patients and families must be done with sensitivity and confidentiality. Appropriate counseling services should be available regarding the wisdom of choosing genetic testing in the first place, and in dealing with the results. Informed consent should be obtained before testing.

Discrimination regarding employment, health, and life insurance is a possible adverse consequence if the results of genetic testing are made public. The Genetic Information Nondiscrimination Act (GINA) of 2008 prohibits discrimination in health coverage and employment based on genetic information. This federal statute defines genetic tests "as an analysis of human DNA, RNA, chromosomes, proteins, or metabolites that detects genotypes, mutations, or chromosomal changes." However, GINA does not protect against discrimination regarding life, disability, or long-term care insurance.

Conclusion

For the moment, most physicians taking care of people with epilepsy rarely need to order genetic tests for diagnosis or clinical management. Dravet syndrome is a notable exception, where early confirmation of the diagnosis may direct treatment and potentially improve prognosis. Prenatal testing has already proven its merits in decreasing the incidence of devastating neurologic diseases such as Tay-Sachs and familial dysautonomia. As more epilepsy-associated genes are identified and genetic mechanisms of epilepsy are elucidated, genetic testing may soon join electroencephalography and magnetic resonance imaging as a useful diagnostic and management tool for the many disorders that constitute epilepsy.

Dr. Wilner also writes the Medscape neurology blog, NeuroNotes, and is the author of *Epilepsy: 199 Answers*.[4]