

## **DOES GENETIC TESTING HAVE A ROLE IN EPILEPSY MANAGEMENT? – NO**

**Nurses Bebek**

Turkey

Many types of epilepsy have an inherited susceptibility. Single gene disorders accompanied by epilepsy with mental retardation and abnormalities of brain structure constitute only 1% of epilepsies such as tuberous sclerosis, subcortical band heterotopia, periventricular nodular heterotopia and progressive myoclonus epilepsies. Complex inheritance underlies the majority of idiopathic epilepsies in which seizures are the prominent clinical features. Besides genetic and phenotypic heterogeneity, multiple genes interact with environmental factors. For these reasons, the evaluation of an epileptic patient with suspected genetic etiology is a complex issue and recent advances in the genetics of epilepsies do not provide clearcut answers at this point.

Mutations in voltage or ligand gated ion channel genes are discovered in a few idiopathic epilepsy syndromes including autosomal dominant nocturnal frontal lobe epilepsy, benign familial neonatal convulsions, generalized epilepsy febrile seizures plus syndromes. These advances suggested that epilepsies could be interpreted as channelopathies. Although many genes have been identified in idiopathic epilepsy syndromes, few of them have clinical utility for diagnostic and predictive purposes. *SCN1A*, *Glut1* are examples of recommended rare gene tests which lead to an early and accurate diagnosis.

Identification of a causative mutation may clarify the etiology and reduce the need for further intensive investigations therefore influencing patient management and genetic counseling. Additionally, the genetic test must be accurate, clinically useful and the potential negative impact must also be considered. Moreover the tests are expensive. Debate about ethical rules, risk of patient stratification are further remarkable issues. Genetic testing is not recommended for everyone with epilepsy but primarily limited to the research area.

At the present time, genetic testing in clinical epilepsy can be performed in suspected cases of severe myoclonic epilepsy of infancy, generalized epilepsy with febrile seizures, atypical cases of benign familial neonatal convulsions and cases of autosomal-dominant nocturnal frontal lobe epilepsy. Autosomal dominant nocturnal frontal lobe epilepsy is an example of focal epilepsy syndrome with monogenic background. Mutations of the neuronal nicotinic acetylcholine receptor are shown. Even in this distinctive clinical entity, molecular testing has relatively low mutation detection rate. Majority of the gene mutations have been identified only in single or a few reports.

Recent investigations showed recurrent microdeletion of chromosome 15q13.3 in 1% of idiopathic generalized epilepsy patients. This microdeletion has been found in patients with schizophrenia as well. Copy number variants (CNVs) are more likely pathogenic if they are larger, but pathogenic CNVs shows considerable variations and greater frequency than previously known susceptibility genes. However this finding does not carry a predictive value, unaffected members in the same family can carry the identical genotype. Benign occipital childhood epilepsies are also typical examples showing complex inheritance.

Genetic testing in clinical practice also play an important role in severe monogenic epilepsy syndromes like epileptic encephalopathies. *SCN1A*; the *alpha-1 subunit of the sodium channel* mutation has a key role in clinical diagnosis of Dravet syndrome. *PCDH19* Encoding *Protocadherin 19* is the gene responsible for epilepsy limited to females with mental retardation.

In the future, elucidation of the association between the epilepsy gene mutations and channel function will increase the value of genetic testing. Pharmacogenetics has been one of the most interesting genetic testing area. Pharmacodynamics and metabolism of the drugs show remarkable racial and individual variations. The relation between HLA-B alleles and medication effects in asian population is an important clue. But, the concept of tailored therapy is not yet applicable.

At present, genetic testing is indicated for specific disorders. The management of an epilepsy patient with suspected genetic etiology is a complex issue that requires complete clinical and electroencephalographic assessment before requesting molecular testing. In general, many clinicians are not aware of the types and availability of genetic tests. Moreover, the genetic diagnosis does not yet lead to the cure of the condition. Although new information is emerging on an almost daily basis, current role of genetic testing has a limited clinical impact in epilepsy management.