Genetic Epilepsies - Recent Developments in Detection and Treatment

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NOW

- Focal epilepsy with MRI-detectable lesions
- Single-gene epilepsies: familial, *de novo*
- Epilepsies with complex inheritance
- Modifiers and susceptibility alleles

THEN

- ‘Idiopathic’
- Congenital lesions
- Birth anoxia
- Other
- Infectious
- Neoplasm
- Stroke
- Trauma

Number of cases: 1975
Idiopathic to Genetic Epilepsy

- As genetic research progresses, the etiology of epilepsy and seizures becomes more well defined
- More research is done every day, even on the “old” genes like SCN1A and TSC
- As more research is done, effects of specific mutations and treatment implications become clearer
- At present, targeted treatments are not available for most genetic epilepsies
Current Research

- Focused primarily on presumed single gene (monogenic) epilepsies
- As gene panels become more comprehensive and specific and that it is more clear exactly what is being measured with each test
  - implications of the results
  - better definition of specific subtypes
  - better information about multigenic epilepsy, and epilepsy susceptibility genes
Inherited Epilepsy

- Mendelian (Monogenic) - Familial
  - Autosomal Dominant
  - Autosomal Recessive
- Non-Mendelian (Polygenic)
- Mitochondrial DNA
- X-Linked
- Predominately Multigenic
Genes Affected- Voltage-Gated Ion Channels

- Voltage Gated Channels - **Voltage-gated ion channels** are a class of transmembrane proteins that form ion channels that are activated by changes in the electrical membrane potential near the channel. The membrane potential alters the conformation of the channel proteins, regulating their opening and closing.
  - Sodium
  - Calcium
  - Potassium
  - Chloride
Genes Affected - Voltage-Gated Ion Channels
-KCNQ2

- Usually associated with Benign Familial Neonatal Epilepsy
- Also associated with Familial Neonatal Onset Epileptic Encephalopathy
- Class IV evidence of beneficial treatment with Retigabine/Esogabine, a KCNQ Channel agonist
Genes Affected- Voltage-Gated Ion Channels - SCN1A

- Most Common Epilepsy Gene - variants present in a wide range of focal and generalized epilepsies
- Missense and Nonsense mutations ~2 to 3% - Dravet Syndrome and GEFS+
G Protein Related Ion Channels - GNAO1

- Ohtahara Like Syndrome
- Epileptic Spasms
- Movement Disorder
- Encephalopathy

GNAO1 mutations in epileptic encephalopathy

Effect: Inhibition of voltage-gated Ca²⁺ channels, activation of K⁺ channels
Genes Affected - Ligand-Gated Ion Channels

- Ligand Gated Channels - **Ligand-gated ion channels** are a class of transmembrane proteins that form ion channels that are activated or inhibited by neurotransmitters that bind to the **channel**. The ligand alters the conformation of the channel proteins, regulating their opening and closing.
  - GABA
  - Glutamate (NMDA, AMPA, Kainate)
  - Acetylcholine
  - Glycine
  - Serotonin
**Genes Affected - Metabolic**

ONE example is GLUT1 (SLC2A1)

Difficult to control seizures;
developmental delay;
Treatment is much improved with use of ketogenic diet.
Complex Metabolic

mTOR associated with TSC and Familial Cortical Dysplasia
Neuronal Synaptic Proteins-ARHGEF9

- Encodes Collybistin a brain specific nucleotide exchange factor (GTP-ase)
- Role in the formation of Glycine and GABA receptors
- Associated with Infancy onset delays in intellectual and motor development, refractory seizures
Genes Affected
Gene Expression - MeCP2

Not just for Girls anymore
Rett Syndrome - Mostly Girls
MeCP2 Duplication Syndrome - Severe developmental delay and regression; seizures; hypotonia in childhood progressing to hypertonia
Atypical Rett Syndrome

- Other DNA expression genes
- CDKL5; FOXG1; MECP2; MEF2C
CDKL5 Epileptic Encephalopathy - Atypical Rett

- Cyclin Dependent Kinase Like (CDKL)
- X Linked - Boys More severely affected than girls
- Neonatal Hypotonia
- Focal Seizures at 4 weeks to 6 Months
- Infantile Spasms
- Later - Treatment resistant myoclonic epilepsy; movement disorder
Same Gene - KCNT1 - Differing Syndromes

Autosomal Dominant Nocturnal Frontal Lobe Epilepsy - ADNFLE
Malignant Migrating Partial Seizures of Infancy - MMPSI

*KCNT1* mutations in ADNFLE and MMPSI
Deciding and Counseling Prior to Genetic Testing
Consideration of Tests to be Obtained

- What is the question to be answered?
- How is the answer to be used?
- What are the implications for the family?
- What are the ethical implications for the patient?
Questions to be Answered

• What is the cause of the epilepsy or epilepsy syndrome?
• Is it a KNOWN genetic cause of epilepsy?
• How will false positive results be assessed?
• Are future children likely to be affected?
• Will the presence of the gene in asymptomatic siblings confer an increased risk to their children?
Questions to be Answered

- Families and patients need to understand the concepts of sensitivity (false negatives) and specificity (false positives)
- Prior to the test, counseling for the patient and family regarding exactly what the implications of a positive or negative test will be or will not be
- Counseling for the patient and family regarding the possibility of a de novo mutation vs incomplete penetrance
How is the Answer to be Used?

• Reproductive decisions
  • Further children
  • Younger siblings
  • Children of unaffected siblings
  • Reproductive decisions for the patient
• Treatment decisions
  • Useful treatments
  • Treatments to be avoided
How will the Answer be Used?

- The result must ultimately benefit the patient
  - Treatment
  - Prognosis
- The result may cause anxiety or guilt in family members and these issues must be addressed prior to the testing
- It should be made clear to everyone in the family that no one is to blame and no one has control over their genetic makeup
- Adequate information should be made available to the patient and family regarding reproductive implications
What are the implications for the Family?

• Patients and family members must be encouraged to communicate freely about how they feel about the testing and what is expected from the results.

• Patients and family members may have unrealistic expectations regarding the results - testing is available from many commercial sources

• It is an entirely normal response to feel blame or guilt regarding the results of genetic testing

• Prior to the testing, families need to understand the insurance approval process
Ethical Considerations for the Patient

- Will the test benefit the patient?
- Will the test result in potential harm to the patient? Insurability, anxiety about reproductive fitness, anxiety about others knowing (employers, friends, family members)
Conclusions

- Genetic effects on epilepsy are very common and may affect most patients.
- Knowledge related to treatment of genetically caused epilepsy is extremely limited.
- Genes responsible for epilepsy can have myriad presentations even in the same family due to penetrance and other modifying factors.
- Expectations of the patient and the family need to be carefully managed using thorough genetic counseling and ongoing communication both before and after the test results are obtained.