An Update in Genetics of Epilepsy

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Outline

• Overview of Genetics

• Role of Genetics in Epilepsy
  – Implications for Patients/Families

• Advances in Genetics of Epilepsy and Genetic Testing
Overview of Genetics

• What is Genetics?

  Study of heredity or how traits are passed from parent to child
Overview of Genetics

• Traits:
  – Notable feature or characteristic in a person
  – Each person has a different combination of traits which makes us unique
Physical Traits
Physical Traits
Examples of Traits:

• Height, body weight, health or disease

• Genetic and environmental contribution
Examples of Traits:

• Height, body weight, health or disease

• *Genetic* and environmental contribution
Gene

- Basic unit of heredity
- Made of lengths of DNA (deoxyribonucleic acid)
- Genes → proteins → normal body function
Human Genetic Make-up

- ~20,000 genes
- The entire collection of DNA is called your Genome
Human Chromosomes

1 2 3 4 5
6 7 8 9 10
11 12 13 14 15
16 17 18 19 20
21 22

Female

OR

Male
Sex Chromosomes
DNA, genetic code and making of human protein for normal function of human body
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Linkage Analysis

Early Epilepsy Gene Discovery
Types of Genetic Disorders in Epilepsy

- Single Gene
- Chromosome
- Complex
- Mitochondrial
Genetic Changes that can Predispose to Epilepsy: Single Gene
Single Gene Epilepsy Disorders

- caused by changes (mutations) in single genes
- recognizable inheritance pattern (dominant, recessive, X-linked) or arise by new mutation or de novo
- very few cause primary epilepsy syndromes
  - Childhood Absence Epilepsy
  - Juvenile Myoclonic Epilepsy
- many more will frequently have epilepsy as one of their symptoms
Features of the single gene epilepsy disorders

• same gene mutation may produce multiple different seizure types or severity

• not all individuals inheriting the affected epilepsy gene will develop seizures

• more than one gene can cause the same disorder
Types of Genetic Disorders in Epilepsy

• Single Gene
• Chromosome
• Complex
• Mitochondrial
Genetic Change that can Predispose to Epilepsy:
Loss of part of a chromosome
Chromosome Disorders

• result in loss (deletion) or extra (duplication) chromosome content

• often new change in child so recurrence risk is low, but if present in parent then recurrence risk is 50%

• often associated with other medical problems
Types of Genetic Disorders in Epilepsy

• Single Gene

• Chromosome

• Complex

• Mitochondrial
Complex Disorders

• many epilepsies with a genetic basis
  – Childhood Absence Epilepsy
  – Juvenile Myoclonic Epilepsy

• interactions between multiple genes with or without environment

• pattern of inheritance less clear
Types of Genetic Disorders in Epilepsy

• Single Gene
• Chromosome
• Complex
• Mitochondrial
Mitochondrial Disorders

- mitochondrial DNA is passed from mother to child
- every child of a mother carrying mitochondrial DNA mutation is at risk of being affected
- affects multiple organs within the body
- symptoms vary amongst individuals
Mitochondrial Disorders

- Affected
- Abnormal Mitochondria
- Normal Mitochondria

Pedigree diagram showing the inheritance pattern of mitochondrial disorders.
Question:

If a parent or child has epilepsy, what is the risk to other family members?
Cause is Known

Acquired brain injury including stroke, brain tumor, brain infection or severe head trauma

Risk is not significantly increased
Cause is Known

Genetic Disorder (single gene, chromosome, mitochondrial)

Risk will depend on genetic cause
Single Gene Disorders

• New dominant mutation recurrence risk is low – severe epilepsy disorders

• If not new, depends on inheritance pattern
  – Dominant, recessive, X-linked
Dominant Inheritance: 50% risk
Recessive Inheritance: 25% risk
X-linked Inheritance: 50% risk to have an affected son
Cause Unknown

• Many of epilepsy syndromes with genetic basis (Childhood Absence Epilepsy)

• Complex inheritance

• Risk is an estimate based on past studies
Estimated Risks

• Risk in close relatives is about 2 to 4 times higher than people in general population

• Risk is less than 1 in 10 that a child of a person with epilepsy will also develop epilepsy

• Risk is higher in relatives of a person with generalized epilepsy, young onset epilepsy and mothers vs fathers with epilepsy
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Epilepsy Genetics and Genomics – Now

• Chromosome Microarray or Array Comparative Genomic Hybridization (CGH)

• Next-Generation Sequencing
Methods: Array CGH

DNA fragments

Hybridize 1:1 Ratio

Patient DNA

Normal Control DNA

From http://www.utoronto.ca/cancyto
Examining chromosomes or genomes for genomic imbalances or Copy Number Variants (CNVs) causing Epilepsy
Copy Number Variants

- Deletion or Copy Loss

Original Chromosome

- Duplication or Copy Gain

Deletion

Duplication
Chromosome Microarray in Epilepsy: What have we found?

- A cause or abnormal CNV is identified in up to 15% of patients
  - Treatment resistant epilepsy or other severe forms of epilepsy
  - Epilepsy plus other neurological problem or birth defect

- A cause is identified less often in patients with benign epilepsy syndromes (Juvenile Myoclonic Epilepsy)
Chromosome Microarray in Epilepsy: What have we found?

- Limitations to testing: negative test does not rule out genetic cause

- Results of unclear significance

- Incidental findings: finding an abnormality in a gene predisposing to unrelated health problem (example breast cancer gene)
Chromosome Microarray in Epilepsy: Who should be Tested?

• Cause of Epilepsy is unknown and:
  – a more severe form of epilepsy or
  – epilepsy plus global delay, intellectual disability, autism, other neurological problem and/or birth defect

• Patient and/or Family who has received appropriate genetic counselling
Epilepsy Genetics and Genomics – Now

- Chromosome Microarray or Array Comparative Genomic Hybridization (CGH) and Copy Number Variants
- Next-Generation Sequencing
Examining genes, exomes and genomes for sequence variants causing Epilepsy

Sanger sequencing

Next-generation sequencing
Next-generation sequencing

- Massively parallel sequencing

- Sequence millions of fragments simultaneously

- Whole genome, exome (protein coding), targeted or gene panels
Whole genome, exome or targeted sequencing in Epilepsy

Whole Genome

Exome = 1%

Targeted = 10 to 500 epilepsy genes
Whole Exome sequencing

- 20,000 variants per individual
- Exome contains 85% of disease-causing mutations
Next Generation Sequencing: What is the impact?

Rapid increase in Gene Discovery
Next Generation Sequencing: Epilepsy Impact

• ~ 500 genes associated with epilepsy

• Significant increase in diagnoses:
  – Diagnosis 10 – 50% of those tested
  – Severe epilepsy conditions or Epilepsy plus
  – New dominant mutations in multiple different genes
Next Generation Sequencing: Challenges

- Negative test does not rule out genetic cause
- Variants of unclear significance
- Proving new or novel gene identified is the cause of epilepsy
- Availability in Canada
- Ethical Issues
- Cost
Whole Genome Sequencing

Cost per Genome

Moore's Law

NIH National Human Genome Research Institute

genome.gov/sequencingcosts
Next Generation Sequencing: Positive Impact on Patients/Families

• Earlier diagnosis including disorders with specific treatment implications

• More accurate counselling regarding outcome and recurrence risk

• Prevent additional investigations

• A clear genetic diagnosis improves access to therapies/community support
Next Generation Sequencing: Negative Impact on Patients/Families

- Identifying a disease without specific treatment

- Discrimination regarding life, disability or long-term care insurance

- Incidental findings (finding an abnormality in a gene that increase risk for developing cancer)

- Genetic Counselling Before Testing
Genetic Testing in Patients/ families with Epilepsy

Chromosome Microarray Analysis:

• Available in BC
• Indicated in patients with epilepsy of unknown cause and:
  – Severe forms of epilepsy
  – Epilepsy plus delay, intellectual disability, autism, other neurological/behavioral problems and/or other congenital abnormalities
• **Pre-test genetic counselling required**
Genetic Testing in Patients/families with Epilepsy

Next Generation Sequencing:

• Limited Availability in BC
  – Research, MSP funding
• Consider in patients with negative chromosome microarray and:
  – Severe forms of epilepsy
  – Epilepsy Plus
  – Early onset epilepsy

• Pre-test genetic counselling required
Future Directions

• Standardized approach to genetic testing

• Genetic discoveries leading to development of better treatment options
Future Directions

Pharmacogenomics of Epilepsy:

• The study of the interaction of an individual's genetic makeup and response to a drug.
  – Adverse drug reactions (*HLA-B*1502)
  – Seizure control

• Aim to individualize and optimize treatment based on genetic make-up
Summary

• Genetic factors play a role in many epilepsy disorders

• New technology (Chromosome Microarray and Next-Generation Sequencing) has revolutionized gene discovery and genetic testing in epilepsy

• Recent discoveries and further advances in diagnosis and pharmacogenomics will likely lead to improved individualized treatment of epilepsy
Questions?
Acquired (low)

Epilepsies with a major acquired cause (e.g., trauma, hypoxia, vascular etc)

Genetic (high)

Number with Epilepsy

Epilepsies with Complex inheritance

Single-gene epilepsies

Genetic Contribution to Epilepsy