Genetics of Epilepsy
Introduction and overview

Ki Joong Kim MD PhD
Pediatric Neurology
Seoul National University Children’s Hospital
Seoul, Korea
Role of genetics in epilepsy

\[
\begin{align*}
\text{Idiopathic} & \rightarrow \text{genetic (+ unknown)} \\
\text{Symptomatic} & \rightarrow \text{structural / metabolic} \\
\text{Cryptogenic} & \rightarrow \text{unknown}
\end{align*}
\]

Genetic epilepsy

epilepsy is direct result of known or presumed genetic defect(s)
in which seizures are core symptom of disorder
Categories of genetic epilepsies

- Initiating Event
- Critical Modulators
- Structural Functional Changes
- Clinical Seizures

Altered structures:
- MTLE, HIE Post-encephalitic

Altered functions:
- MCD, TS / NF, FCD
- Genetic disorders with epilepsy
- Primary genetic epilepsy syndromes

White HS Neurology 2002; Vigevano F J Child Neurol 2002
Mendelian vs. complex

**MENDELIAN EPILEPSIES**

LAFFORA’S DISEASE → Deletions, nonsense and missense mutations eg, EPM2A of Lafora’s PME → Altered protein structure eg, Laforin/DSP → Altered protein function eg, Laforin/DSP → Disease phenotype

**GENETICALLY COMPLEX EPILEPSIES**

IGEs → Missense mutations eg, CLCN2 → Altered protein structure → Altered protein function → Disease phenotype

IGEs → Disease-causing variants/polymorphisms eg, CLCN2 → Altered protein function

SMEI → De novo mutations eg, SCN1A → Altered protein structure → Altered protein function → SMEI disease phenotype

GEFS+ → Missense mutations eg, SCN1A → Altered protein structure → Altered protein function → GEFS+ phenotype

Delgado-Esqueta AV et al Epilepsia 2003
Epilepsy genetics began with JME

- Linkage to HLA region of Chr6 (EJM3)
  
  Delgado-Escueta AV Epilepsia 1989  
  Durner M Neurology 1991  
  Sander T Neurology 1997

- No evidence for epilepsy locus in Chr6 HLA region

  Whitehouse WP Am J Hum Genet 1993

- Major susceptibility locus on Chr15q (EJM2)

  Elmslie FV Hum Mol Genet 1997
NEW genetic epilepsy syndrome “GEFS+”

Linkage to 19q13.1 1997
Mutation in voltage-gated Na⁺ channel β1 subunit gene (SCN1B)
Mutation in voltage-gated Na⁺ channel α1 subunit gene (SCN1A)

- AD inheritance
- Phenotype
  - FS
  - FS+
  - FS+ & absences
  - FS+ & myoclonic
  - FS+ & atonic
  - MAE
**Genetic study of epilepsy in the past**

Based on Mendelian genetics
Usually AD inheritance
Genes encoding subunits of ion channels or neurotransmitter receptors

- Ascertainment of large pedigrees
- Linkage analysis of polymorphic markers
- Established disease-associated loci
- Positional cloning to identify pathogenic gene mutation
Major epilepsy genes

Poduri A and Lowenstein D Curr Opin Genet Devlop 2011
**Genotype-phenotype correlation**

- Different subunit mutations $\rightarrow$ same syndrome
- Different channel mutations $\rightarrow$ same syndrome
- Same channel mutations $\rightarrow$ different syndrome
Recent advances in genetics of epilepsy (I)

- Mendelian genetic studies
- Studies of previously discovered genes
- Genes encoding proteins in novel pathways
- Copy number variation (CNV)
Recent advances in genetics of epilepsy (II)

- Genetically determined interneuronopathy \textit{ARX}
- New epilepsy genes \textit{STXBP1 PCDH19}
- Cortical malformation genes \textit{ASPM CDKL5 PNKP TUBA1A}
- Structural genomic variations
- Genome-wide association study

\textit{Poduri A and Lowenstein D Curr Opin Genet Devlop 2011}
Future perspectives of epilepsy genetics

Large consortium + Powerful bioinformatics

Massively parallel sequencing strategies
whole exome/genome sequencing
Summary: Evolution of epilepsy genetics

Past
- Ion channel and neurotransmitter receptor subunits

Present
- Newly discovered genes and novel pathways
- Copy number variations

Future
- Evolving genotype-phenotype correlation
- More mutations, non-coding variants and CNV

Poduri A and Lowenstein D Curr Opin Genet Devlop 2011
Genetics in epilepsy: recent update

Advances on the genetics of Mendelian idiopathic epilepsies

Michel Baulac (France)

Advances on cytogenetics of epilepsies

Byung Chan Lim (Korea)
Thank You for Your Attention