Gene Mapping in Complex Epilepsies

Jocelyn F. Bautista, M.D.
Cleveland Clinic

Monogenic vs. Complex Disease

- Monogenic disease = single gene of “major effect”
- Complex disease = multiple genes of “minor effect” + environment
- Genetic architecture: rare vs. common variants
- Analytical approach: genome-wide vs. candidate gene; linkage vs. association

Dissecting Complex Disease

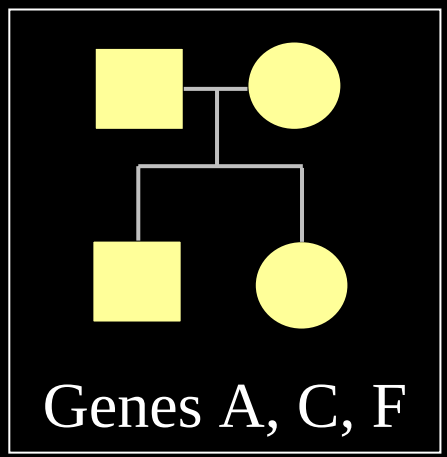
Linkage Analysis

- Family-based
- Locates disease-causing genes by analyzing DNA segments that are co-inherited with the disease
- Very successful for monogenic disease

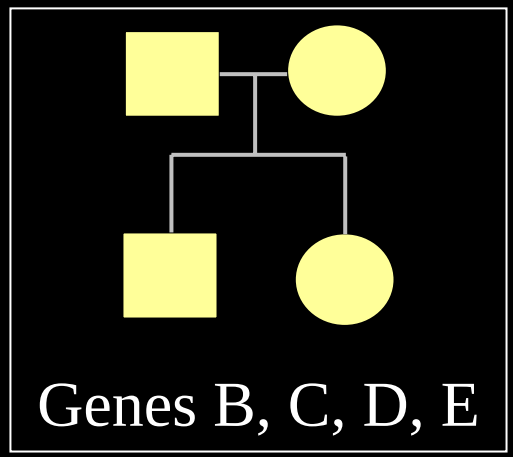
Association Studies

- Case-control or family-based
- Locates disease-causing genes by determining which DNA segments are more common in cases vs. controls
- Not able to detect rare variants

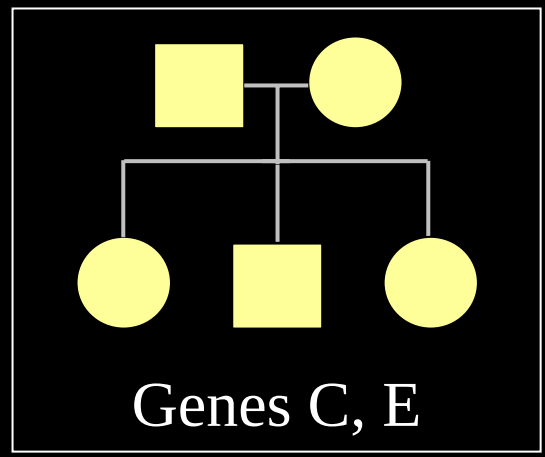
Genetic locus heterogeneity



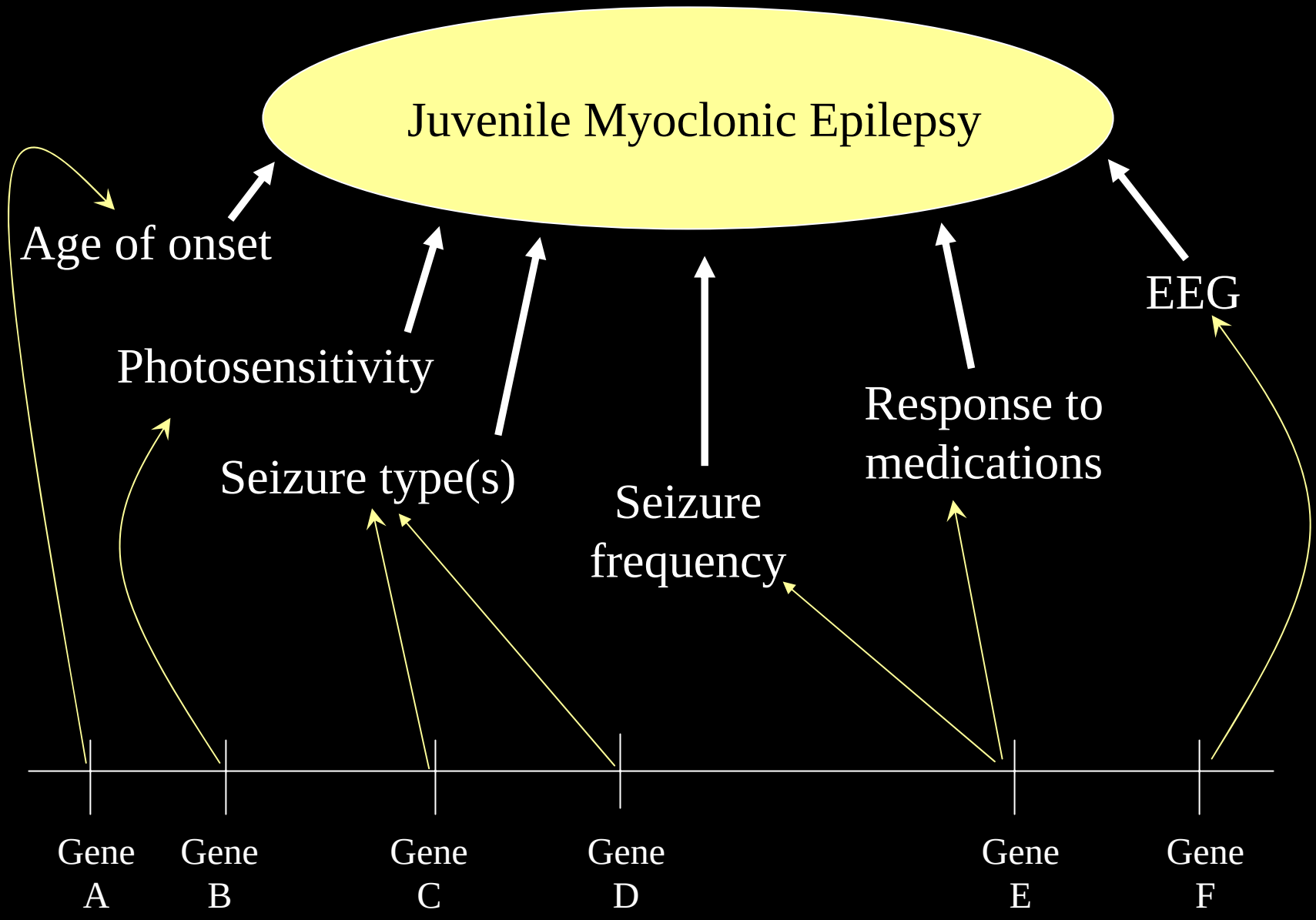
Genes A, C, F



Genes B, C, D, E

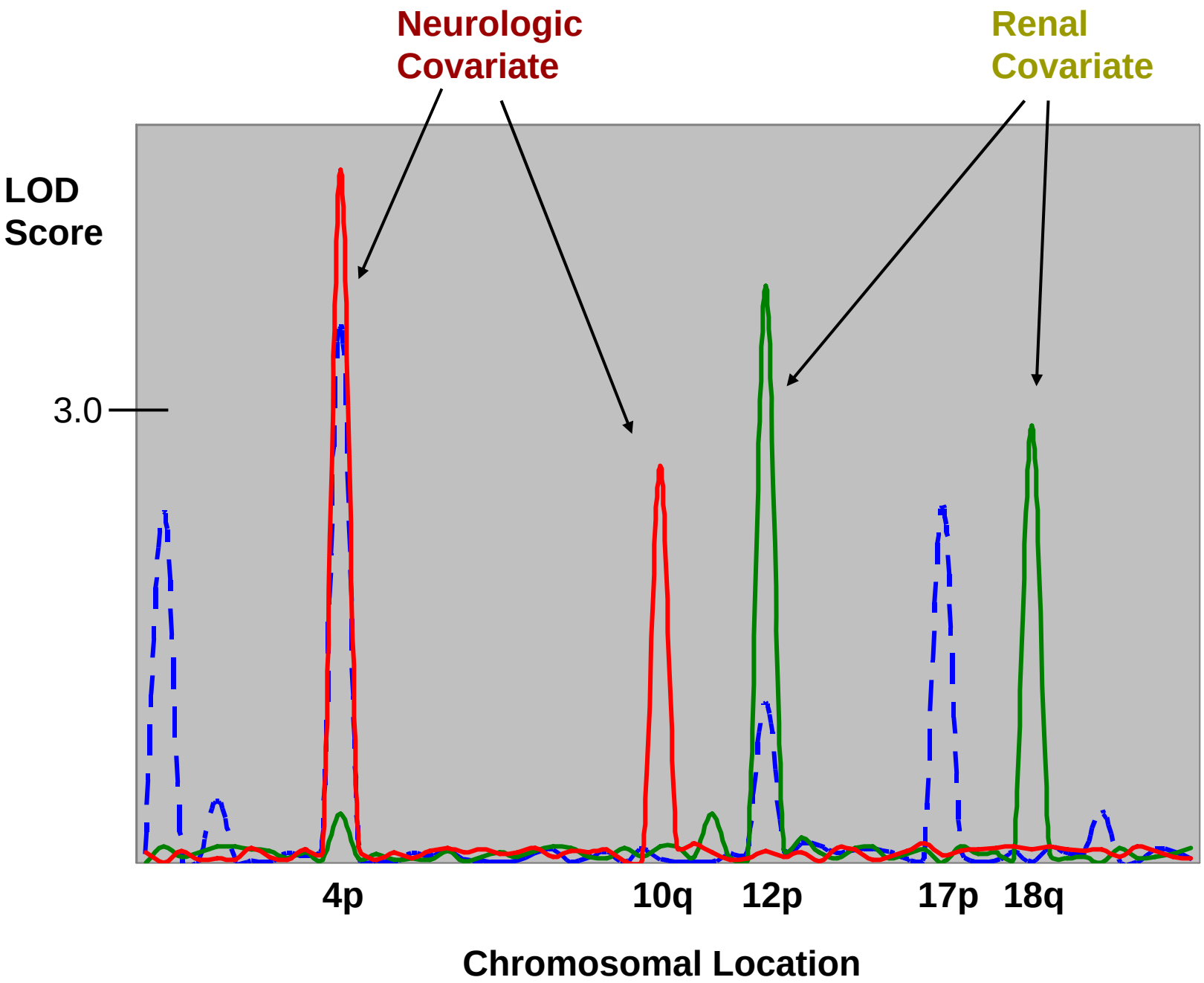


Genes C, E


Juvenile Myoclonic Epilepsy
Age of onset
Photosensitivity
Seizure type(s)
Seizure frequency
Response to medications
EEG
Gene A
Gene B
Gene C
Gene D
Gene E
Gene F

Covariate-based Linkage Analysis

- Modifications to allow for genetic heterogeneity
  - Nonparametric linkage analysis with covariates (clinical phenotypic variables)
  - Allows detection of genetically distinct subtypes based on the covariates chosen
- Choice of covariates
  - Guided by biology, epidemiology


Neurologic Covariate
Renal Covariate
LOD Score
3.0
4p
10q
12p
17p
18q
Chromosomal Location

Dissecting Complex Disease

- Linkage analysis with covariates increases power to detect linkage
  - allows detection of genetically distinct subtypes based on the covariates chosen
- Choice of covariates
  - those with greatest familial correlation
  - identify endophenotypes that are more likely to be genetically determined

Dissecting Complex Disease

Future Opportunities

Refining the phenotype

- imaging, pathology, cellular and molecular endophenotypes

Implementing new analytical techniques

- genome-wide association studies

Analyzing epigenetic effects

- parent-of-origin effects; imprinting

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