Monogenic epilepsies and epilepsy/malformation syndromes

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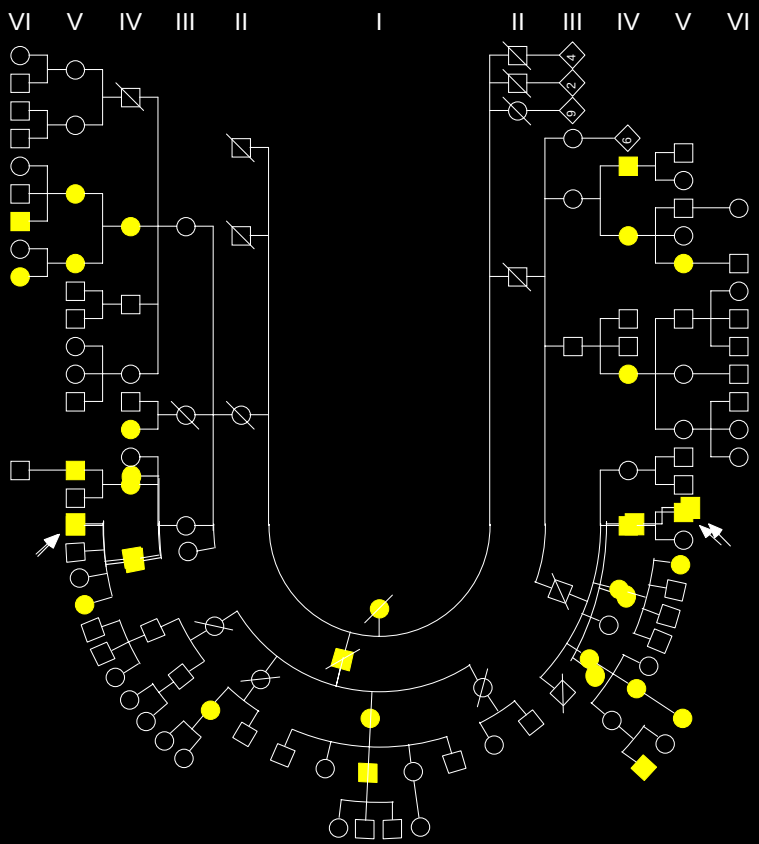
An alternative and accessible version of this presentation is available at 10:10 am in the Videocast of Day One

Monogenic disorders

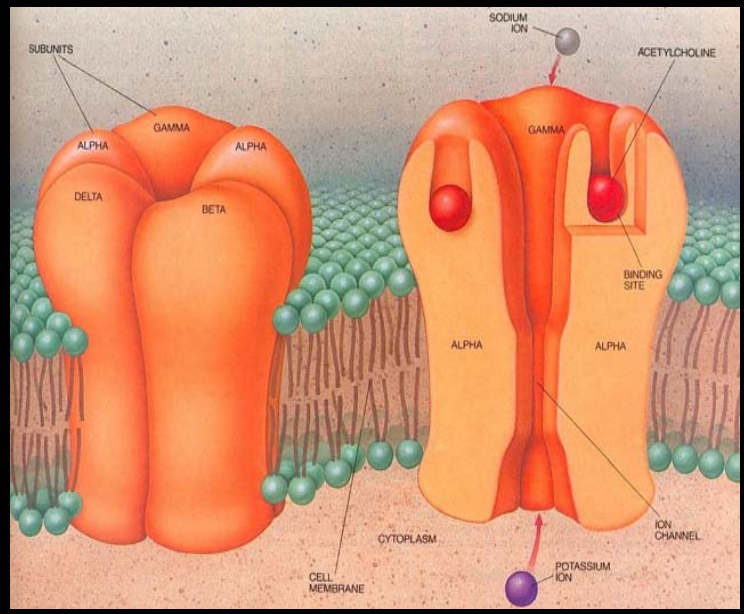
- Conventional approaches provide robust method of gene identification
- Clinical genetics
  - Meticulous phenotyping of large pedigrees
  - Analysis of pedigrees
- Molecular genetics
  - Linkage analysis
  - Mutational analysis



Mapped to 20q

First epilepsy gene (1995)

Nicotinic receptor

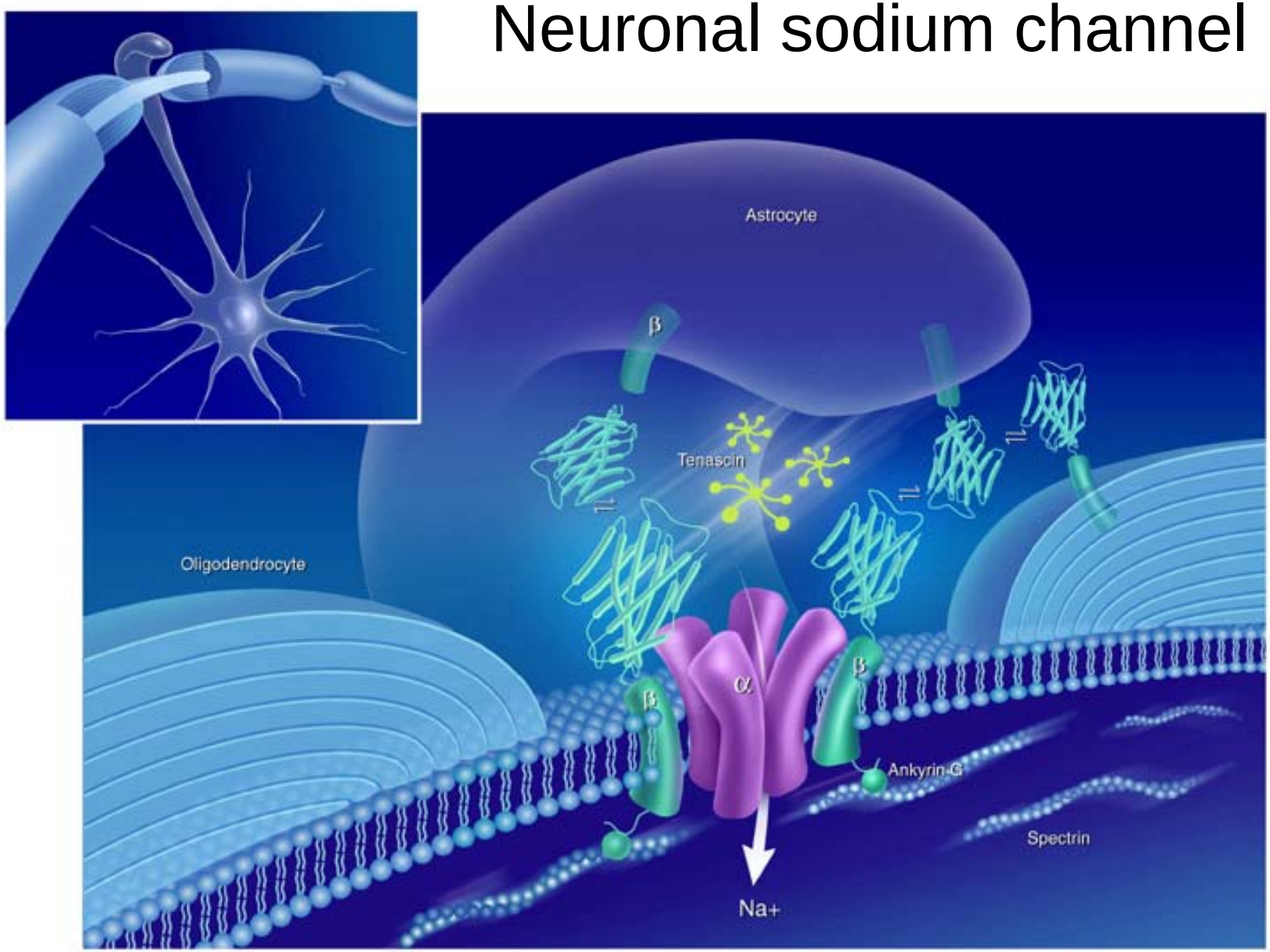


Epilepsy Channelopathies

Idiopathic Epilepsies: Monogenic inheritance 2007

- Voltage-gated ion channel subunits
  - Sodium - GEFS^{+}, Dravet, infantile seizures
  - Potassium - neonatal seizures, absence epilepsy
  - Calcium - absence epilepsy
- Ligand-gated ion channel subunits
  - Nicotinic receptors - frontal lobe epilepsy
  - GABA receptors - GEFS^{+}, absence epilepsy, juvenile myoclonic epilepsy
- Non-ion channel genes
  - *LGI1* - regulates excitatory neurotransmission
- Other genes - *ATP1A2, KCNA1, CRH, KCNMA1*

Neuronal sodium channel



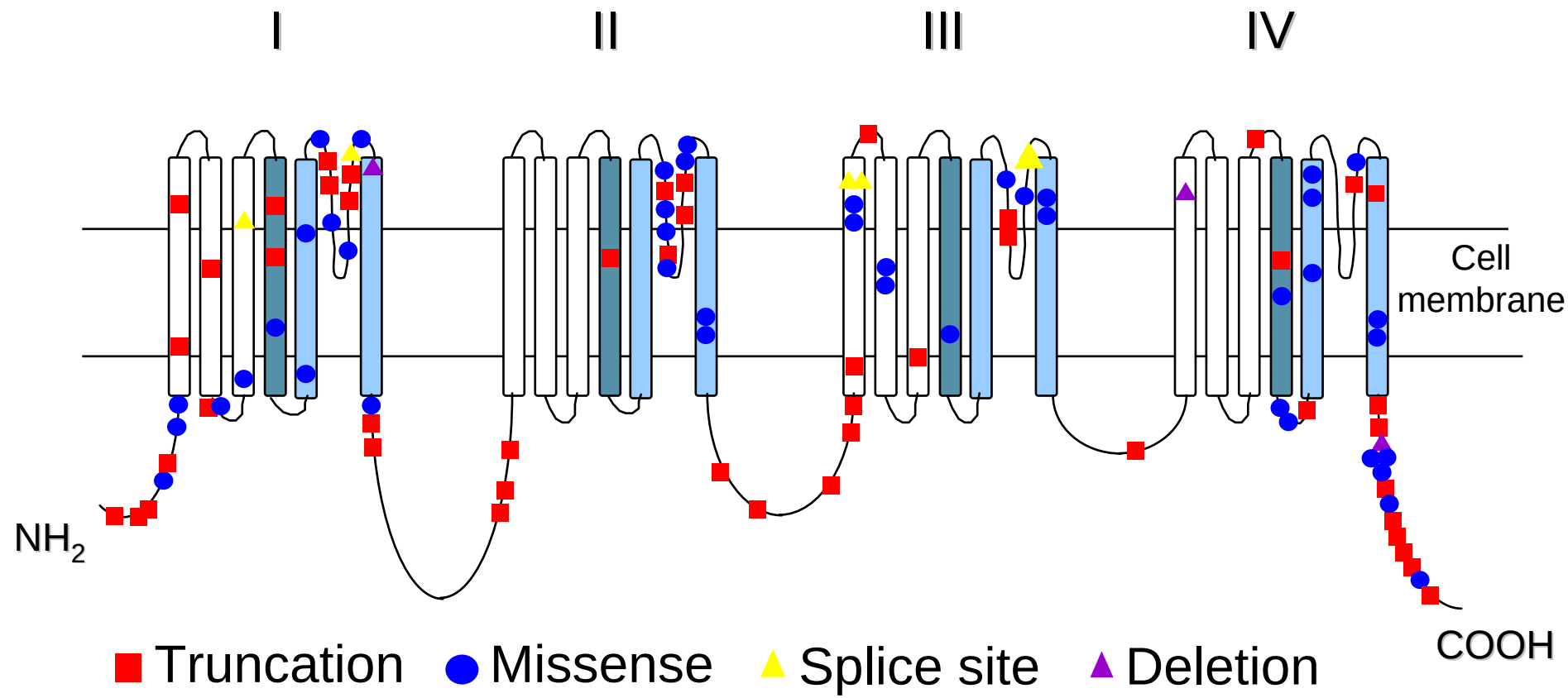
Fundamental Neurology. Editor: Larry R Squire, Publisher: Academic Press

SCN1A channelopathies
α1 subunit of the sodium channel

- Mutations identified in large families with generalized epilepsy and febrile seizures (GEFS+) *(Escayg 2000, Wallace 2001)*

- Found in Dravet syndrome *(Claes 2001)*
  - Devastating syndrome beginning in infancy with prolonged febrile seizures and poor outcome
  - Monogenic cause

SCN1A, sodium channel α1 subunit, mutations in Dravet syndrome *Mulley et al, 2005*



- 70% Dravet children have *SCN1A* mutations
- 95% *de novo*

Endophenotyping of *SCN1A*-channelopathies

Clinical endophenotyping

- Recognize special subgroups
  - "Vaccine encephalopathy" *(Berkovic 2006)*
- Cohort studies to expand phenotypic spectrum
  - Infantile encephalopathies *(Harkin 2007)*
    - New phenotype - Severe Infantile Multifocal Epilepsy

Endophenotyping of *SCN1A*-channelopathies

Molecular endophenotyping

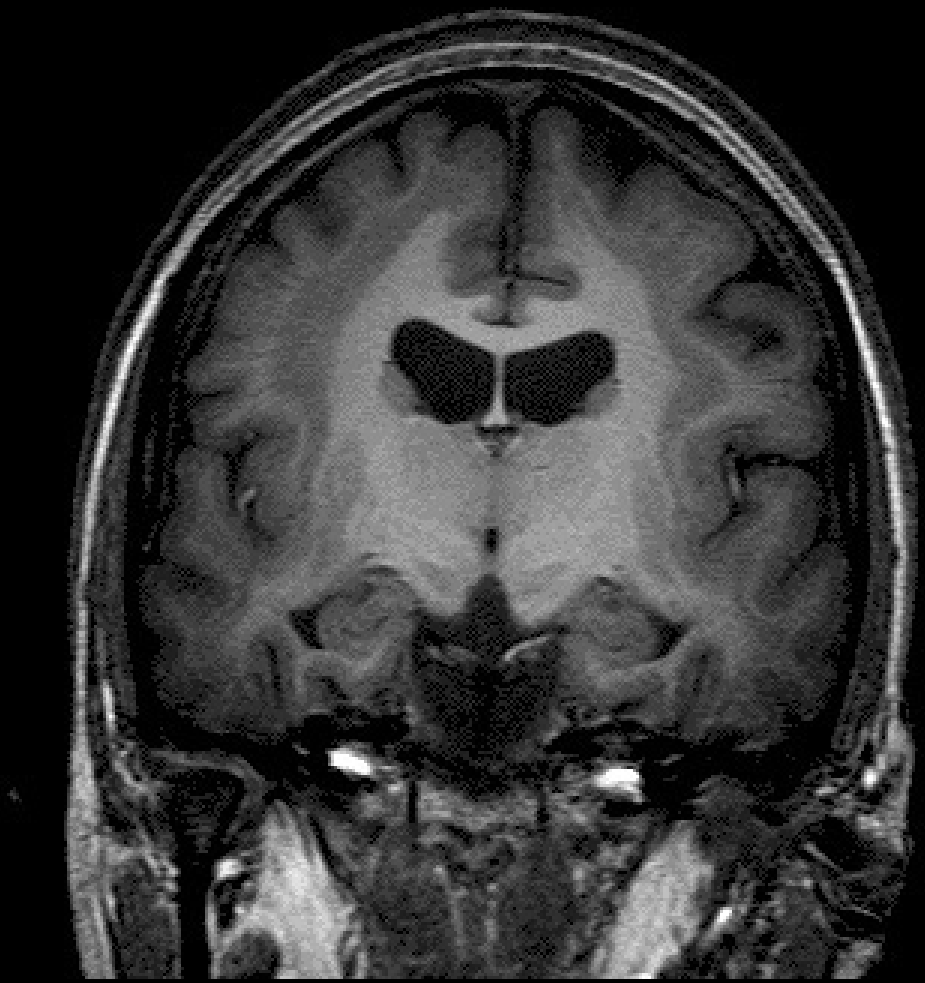
- Novel mechanisms: exonic deletion, submicroscopic deletion
  (Mulley 2006, Suls 2006, Madia 2006)
- Gonadal mosaicism
  (Depienne 2006, Gennaro 2006, Marini, 2006)

Endophenotyping of *SCN1A*-channelopathies

Animal endophenotyping

- *SCN1A* knock out mouse *(Yu 2006)*
  - Sodium current reduced in inhibitory neurons but not excitatory neurons
  - Upregulation of $Na_v1.3$ channels in subset of hippocampal neurons
  - Phenotype varies depending on genetic background

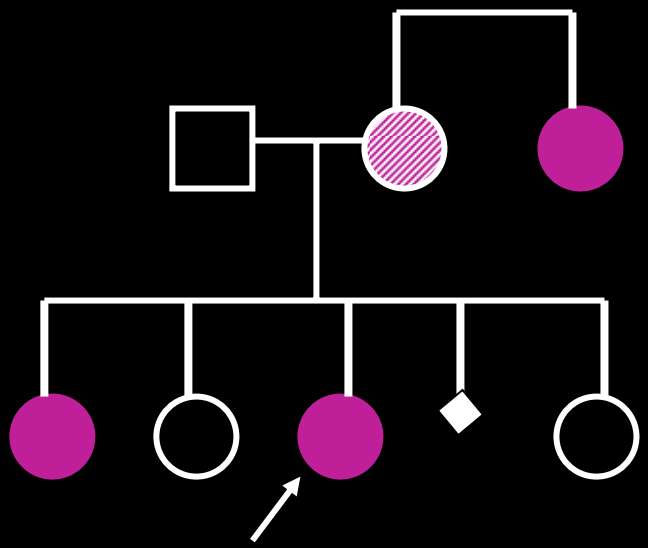
Malformations of Cortical Development

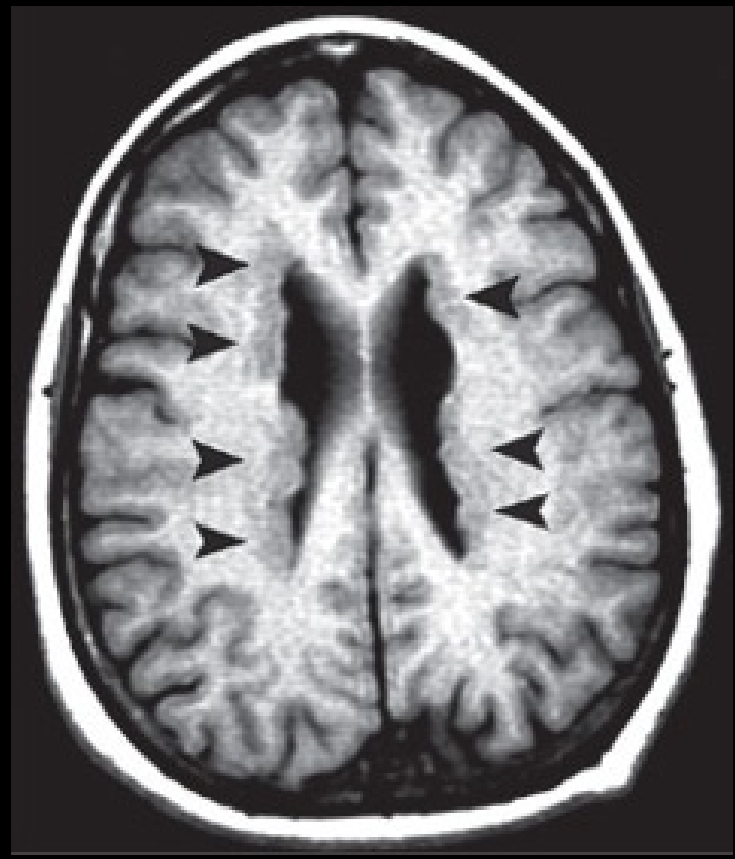


Malformations of cortical development

- Rare disorders
- Many have severe phenotypes with intractable epilepsy and mental retardation
- Collaborative collections of homogeneous phenotypes highly successful
- Links between human phenotypes and animal models deepen scientific understanding
- Some present as “idiopathic epilepsies” and have important genetic implications

27 yr old drama teacher
- Nocturnal seizure
- Aura felt strange
- Planning a pregnancy





Periventricular heterotopia

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Mutation in *Filamin A*

Fox 1998, Feng 2004

X-linked dominant inheritance
Embryonic lethality in males

Filamin A mutations cause PVH

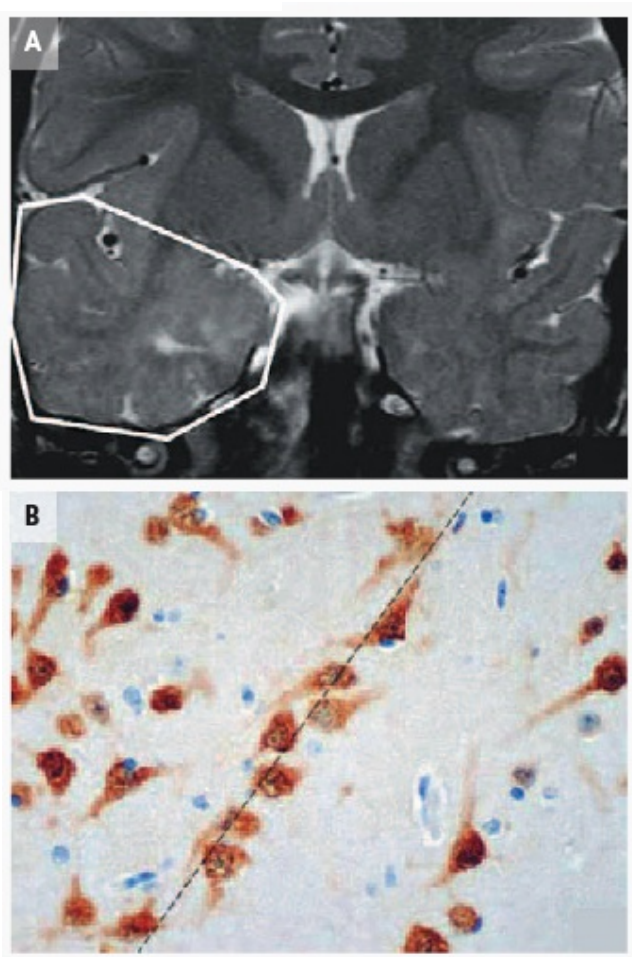
- Filamin A: non-muscle actin-binding protein
- Unusually versatile signalling scaffold
- Mutations disrupt neuronal migration to cerebral cortex and cause cardiovascular defects *(Fox 1998, Moro 2002)*
- Flna knock-out mice die mid-gestation with widespread hemorrhage, cardiac defects *(Feng 2006)*
- Defects in cell-cell contacts and adherens junctions underlie abnormal migration *(Feng 2006)*

N ENGL J MED 354;13 WWW.NEJM.ORG MARCH 30, 2006

Recessive Symptomatic Focal Epilepsy and Mutant Contactin-Associated Protein-like 2

Kevin A. Strauss, M.D., Erik G. Puffenberger, Ph.D., Matthew J. Huentelman, Ph.D., Steven Gottlieb, M.D., Seth E. Dobrin, Ph.D., Jennifer M. Parod, B.S., Dietrich A. Stephan, Ph.D., and D. Holmes Morton, M.D.

- Older Order Amish children
  - Cortical dysplasia-Focal epilepsy
  - Onset 16 months - refractory frontotemporal epilepsy
  - Mild motor delay followed by regression with seizure onset
  - Mental retardation, hyperactive, autistic features
- Cortical dysplasia
  - Abnormal neuronal migration, widespread astrogliosis



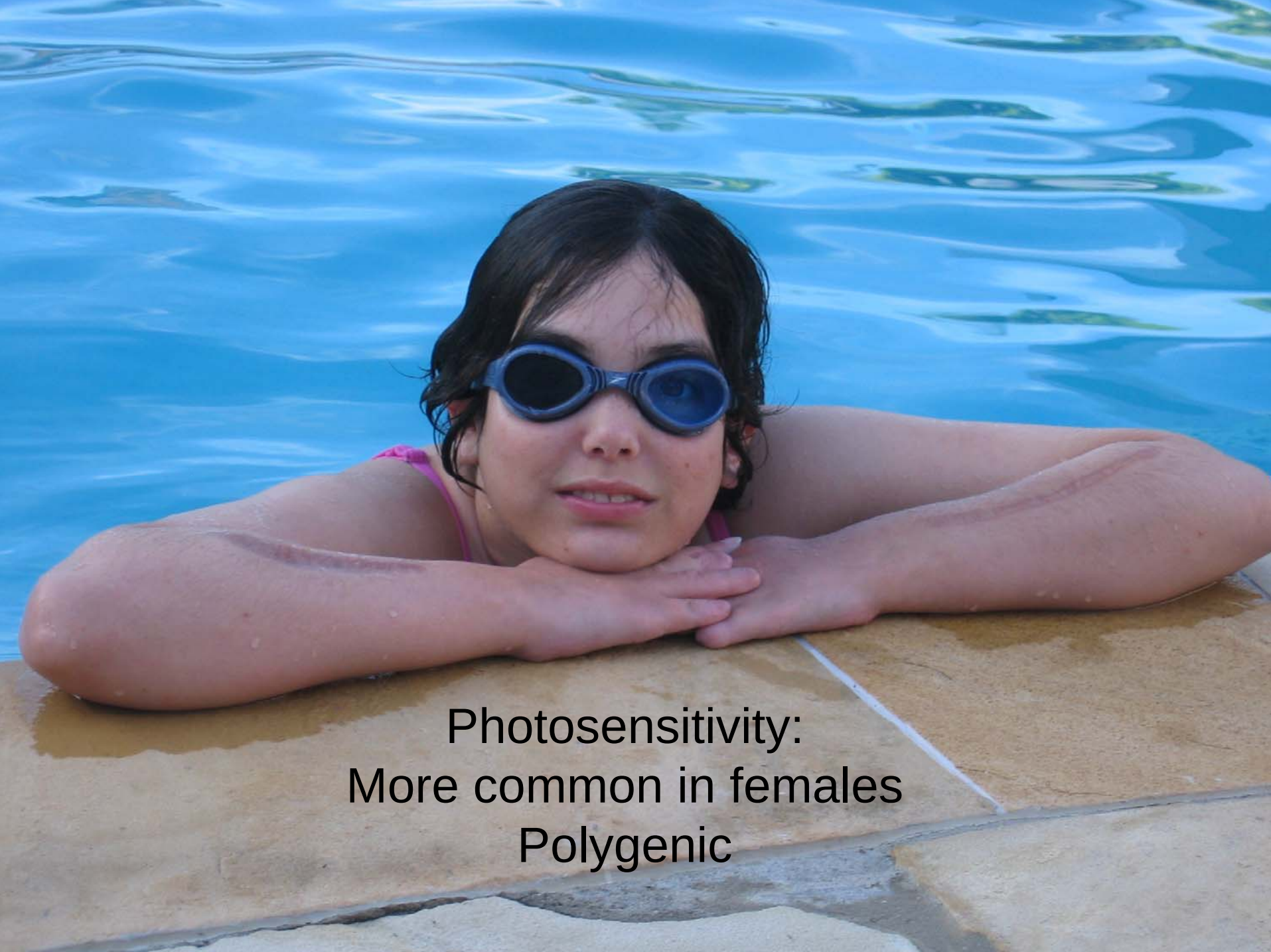
Scaffolding gene for recessive Cortical-Dysplasia Focal Epilepsy

- 10K SNP chip for homozygosity mapping to chromosome 7q36
- Deletion(3709delG) in exon 22 of *CNTNAP2* encoding Contactin-associated protein-like 2 (CASPR2)
- CASPR2 is a transmembrane scaffolding protein and clusters voltage-gated potassium channels (Kv1.1) at the nodes of Ranvier
- Reduced expression of CASPR2 in dysplastic sections

Endophenotyping in the Idiopathic Generalized Epilepsies

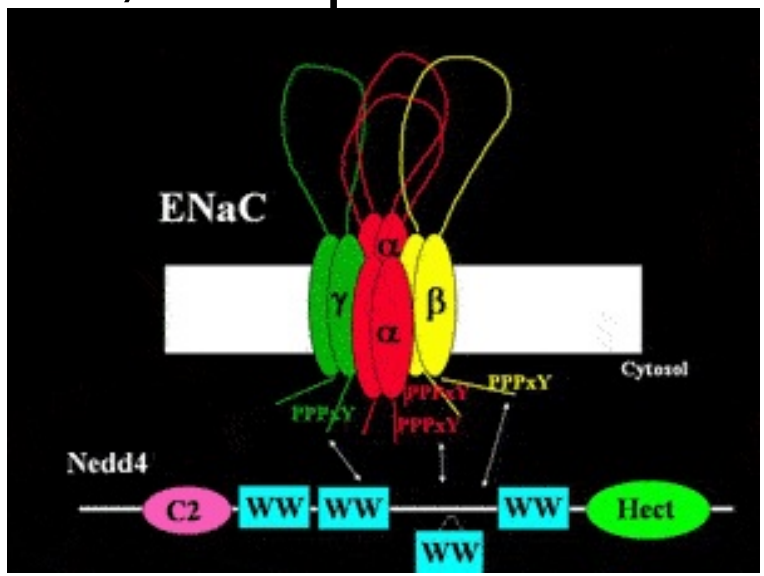
Using monogenic approaches to gain insights into complex disorders

- Syndromes
  - Juvenile Myoclonic Epilepsy
  - Childhood Absence Epilepsy
- Within syndromes: methods to collect more homogeneous phenotypes
- More likely to select genetically homogeneous subgroups


Photosensitivity:
More common in females
Polygenic

Nedd4-2

- Regulates cell surface density of target proteins eg Na+ channels, transporters
- Neuronally Expressed Developmentally-Downregulated



- Encodes a ubiquitin protein ligase
- Catalyzes transfer of ubiquitin to membrane proteins which labels them for degradation
- Role in epilepsy?

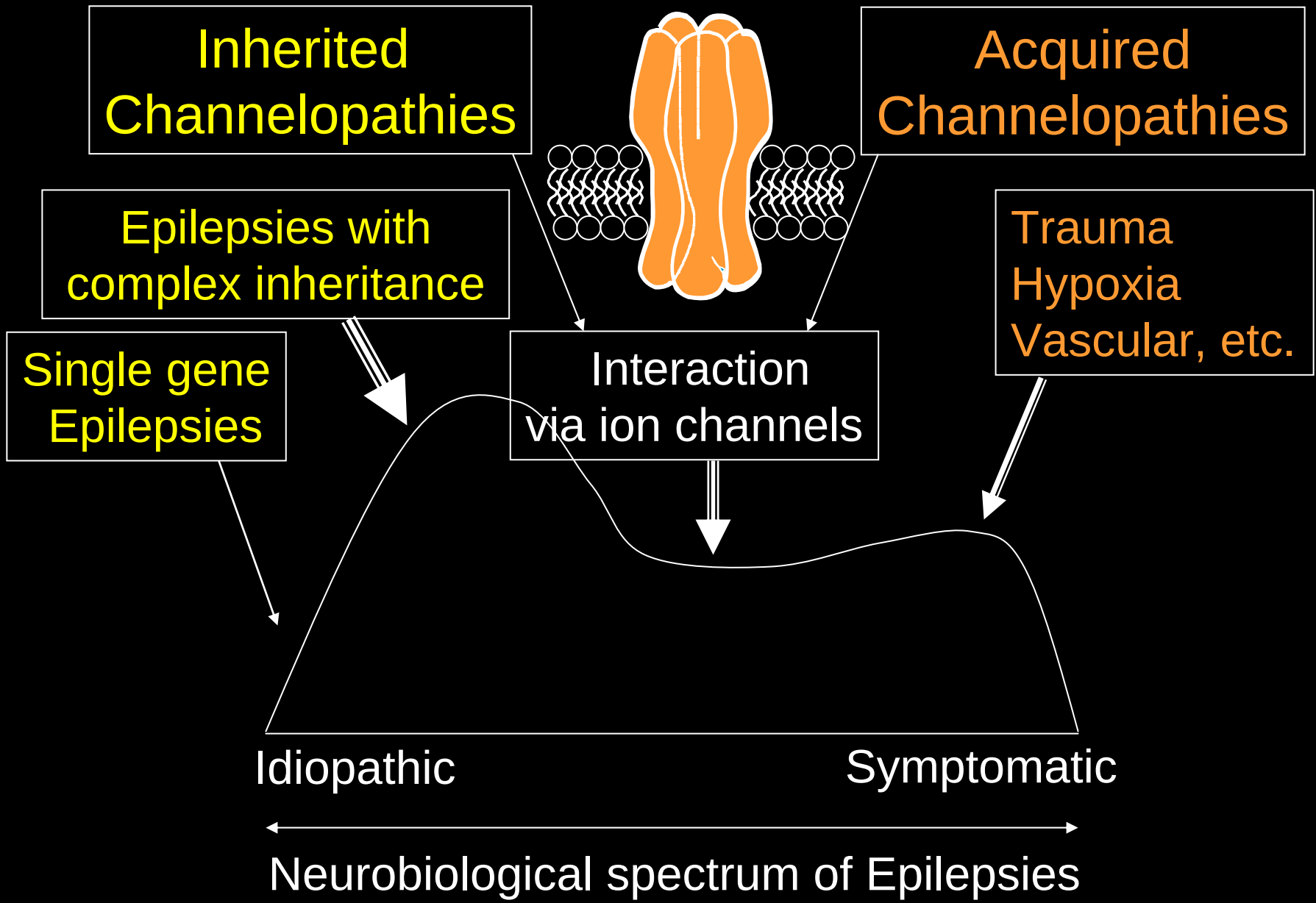
Dibbens et al, Genes, Brain & Behaviour 2007

Nedd4-2

Susceptibility gene for photosensitivity

- Screened 446 individuals from 253 families with generalized epilepsies
- Changes in homogeneous phenotype!
- 3 missense variants in 4/80 photosensitive families (5%)
- Associated with JME with photosensitivity
- *Not* in all affected family members
- Altered conserved amino acids
- Contributes to polygenic aetiology

Dibbens et al, Genes, Brain & Behaviour 2007


Inherited Channelopathies
Acquired Channelopathies
Epilepsies with complex inheritance
Trauma
Hypoxia
Vascular, etc.
Single gene Epilepsies
Interaction via ion channels
Idiopathic
Symptomatic
Neurobiological spectrum of Epilepsies

Conclusions

- Monogenic story far from exhausted
  - New syndromes await discovery
  - Special populations eg. Amish
  - New genes will follow
  - Monogenic genes likely to be relevant to complex epilepsies eg. channelopathies
- Malformation and idiopathic epilepsies may be more related than previously thought…
  - Are subtle malformations seen in idiopathic epilepsies?
  - Genes involved more likely to be structural?

Conclusions

- “Solved” monogenic syndromes have much more to teach
  - Why is intrafamilial variability usual?
  - How do we investigate basis?
    - Modifier genes
    - Environmental effects
- Endophenotyping: clinical, molecular, imaging, animal models
- Deeper level of understanding likely to define new treatment approaches and ultimately prevention of seizure disorders

Thanks to our collaborators