Recent progress in epilepsy genetics

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Background

- State of knowledge
- Top 5 papers of 2008
- Outlook
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Why epilepsy genetics?
Epilepsy genetics in the 21st century

“I am about to discuss the disease called sacred. It is not, in my opinion, any more divine or more sacred than any other diseases, but has a natural cause... Its origin, like that of other diseases, lies in heredity.”

Hippocrates 470-410 BC
Epilepsy genetics in the 21st century

Epilepsy Genetics

- Family aggregation studies
- Family studies
- Twin studies
Why epilepsy genetics?

- **Importance of genetic factors**
  - Heritability of 70%
  - Most obvious in Idiopathic Generalised Epilepsy
  - Also in focal and symptomatic epilepsies

- **Genetic & Family History**
  - Few epilepsies are familial (<1%)
  - Polygenic inheritance in most epilepsies
The history of epilepsy genetics

- **Ion channel concept**
- **ADNFLE**
  - Autosomal Dominant Nocturnal Frontal lobe Epilepsy
- **CHRNA4**
- **SCN1A**
- **SCN1B**
- **GABRG2**
- **IGE**
  - Idiopathic Generalised Epilepsy
  - Generalised Epilepsy with Febrile Seizures Plus
  - (GEFS+)
  - Genetic (Generalised) Epilepsy with Febrile Seizures Plus

Years:
- 1995
- 1998
- 2001
- 2004
- 2007
- 2010
The Channelopathy Concept of the Epilepsies

**Genetic Channelopathies**
- expression of ion channels carrying mutation
- single gene epilepsies
- idiopathic

**Acquired Channelopathies**
- epilepsies with polygenic inheritance
- post-transcriptional modification due to environmental factors
- epilepsies with a major acquired cause trauma, hypoxia, vascular etc.

**Symptomatic**

**Idiopathic**
The history of epilepsy genetics

- "The truth is out there"
- > 100 candidate gene studies with negative results
- Candidate gene approach
- Sample size
- Phenotype definition

Ion channel concept

CHRNA4
SCN1B
SCN1A
GABRG2

IGE
Idiopathic
Generalised
Epilepsy

EFHC1
CACNA1H
EPIGEN

2717 cases
1118 controls
219 genes

today...
State of knowledge

• Importance of genetic factors
• The channelopathy concept
• The “dark ages” of epilepsy genetics
Recent progress in epilepsy genetics

Top 5 papers of 2008
Kapoor et al. 2009

CASR mutations in Idiopathic Generalised Epilepsy
An Idiopathic Epilepsy Syndrome Linked to 3q13.3-q21 and Missense Mutations in the Extracellular Calcium Sensing Receptor Gene

Kapoor et al. 2008
Kapoor et al. 2008

- Three generation Indian family with
  - Various epilepsy phenotypes
  - Linkage to 3q13.3-q21
  - Novel CASR variants
  - CASR variants also in 4/96 IGE patients

- CASR mutations known to affect calcium homeostasis
  - First report on CASR mutations in epilepsy
# 4


*MAGI2* deletions in infantile spasms
Infantile Spasms in Williams Beuren Syndrome

- Critical region for Infantile Spasms
  - *MAGI2* gene
  - Synaptic scaffolding protein
  - Interacts with NMDA receptors
  - Interaction with stargazin

- *MAGI2*
  - a novel gene for Infantile Spasms
Sharp et al. 2008

15q13.3 deletions in mental retardation and seizures

(+ Helbig et al. 2009)
15q13.3 microdeletions

• Newly identified genetic syndrome
• Epilepsy with mental retardation
• Characteristic facial features
• 0.3% of intellectual disability
  – comparable to Angelman, Prader-Willi
Recurrent 15q13.3 microdeletions in IGE

- Identified in two independent cohorts
  - European EPICURE cohort, Mixed 2nd cohort
  - 12/1223 patients, 0/3699 controls, p=5.32 × 10^{-8}

- Deletion spans *CHRNA7*
  - Alpha-7 subunit of nicotinergic acetylcholine receptor
  - Mutation in *CHRNA4, CHRNBP2, CHRNBP2* in ADNFLE

- Identified in other neuropsychiatric disorders
  - ID, schizophrenia, autism, unprecedented spectrum
Recurrent 15q13.3 microdeletions in IGE

- Most common genetic risk factor for epilepsy
  - 1% of patients with IGE
  - Most patients without intellectual disability

- Novel genetic mechanism in common diseases
  - Not restricted to distinct genetic syndromes

- Unprecedented phenotypic spectrum
  - More common in IGE (1%) than in other disorders
15q13.3 microdeletions in IGE

~ 1.5 MB deletion
Saitsu et al. 2008

*STXBP1* mutations in Ohtahara syndrome
Saitsu et al. 2008

• Early infantile epileptic encephalopathy
  – Ohtahara syndrome
  – Severe type of infantile epilepsy
  – Suppression-burst EEG in infancy

• Findings
  – Deletion and mutations of STXBP1 in 5 patients
  – Syntaxin-binding protein 1, synaptic transmission

• \textit{STXBP1}
  – Candidate gene for Severe Infantile Epilepsies
Mefford et al. 2008

1q21.1 deletions in various pediatric phenotypes
Mefford et al. 2008

- Large cohort (> 6000 patients)
  - Mental retardation
  - Isolated cardiac defects
  - Isolated cataracts
  - Autism
  - Seizures
• 1q21.1 microdeletions in 0.5%
  – Various phenotypes including epilepsy
  – not present in > 5000 controls

• Novel paradigm for genetic disease
  – Disease defined by genotype rather than phenotype
  – Statistical association
  – Violates one gene - one disease model

• 1q21.1 microdeletions in various phenotypes
  – A glimpse at the future of human genetics?
Summary - Recent progress & trends

• Familial epilepsies
  – Still possible, but getting fewer
  – Difficulties with functional validation

• Gene findings in rare syndromes
  – Genome-wide screening for microdeletions
  – Follow-up with sequencing

• Association studies
  – Large cohorts
  – Surprising findings
www.epilepsiegenetik.de

PDF