Results of the European Collaborative Project EpiCure: Functional Genomics and Neurobiology of Epilepsies A Basis for New Therapeutic Strategies (EpiCure)

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Disclosure

- Nothing to disclose
Learning Objectives

• Genetic mechanisms for epilepsies and drug refractoriness
• New views on epileptogenesis
• Value of a multicenter integrated project involving clinical and basic research centers
Functional Genomics and Neurobiology of Epilepsies
A Basis for New Therapeutic Strategies

EU FP6 integrated project
Overall Budget € 9,883,261
Four years duration: 2006-2010 (2011)
35 partners from 14 countries
Results published so far in 125 papers
Functional Genomics And Neurobiology Of Epilepsy: A Basis For New Therapeutic Strategies

San Servolo
Venice 2006
SUBPROJECTS

Subproject 1: Genetics of human epilepsies (J. Serratosa and T. Sander)

Subproject 2: Functional consequences of mutations in ion channel genes associated with idiopathic epilepsy and genetically determined pharmacoresistance (M. Mantegazza, H. Lerche)

Subproject 3: Acquired channelopathy and neuronal network reorganisation underlying temporal lobe epilepsy (U. Heinemann, A. Pitkanen)

Subproject 4: Epilepsy and development (R. Guerrini, Y. Ben-Ari)

Subproject 5: Pharmacogenetics of refractory epilepsy, mechanisms of drug resistance and new therapeutic strategies (O. Dulac, H. Beck and E. Perucca)
15q13.3 microdeletions increase risk of idiopathic generalized epilepsy

We identified 15q13.3 microdeletions encompassing the CHRNA7 gene in 12 of 1,223 individuals with idiopathic generalized epilepsy (IGE), which were not detected in 3,699 controls (joint P ¼ 5.32  108). Most deletion carriers showed common IGE syndromes without other features previously associated with 15q13.3 microdeletions, such as intellectual disability, autism or schizophrenia. Our results indicate that 15q13.3 microdeletions constitute the most prevalent risk factor for common epilepsies identified to date.
Meta-analysis of three genome-wide linkage datasets was carried out in 379 IGE-multiplex families of European ancestry including 982 relatives with GGEs.

- The linkage results support an oligogenic predisposition of familial GGE syndromes.
- The genetic risk factor at 5q34 confers risk to a broad spectrum of familial GGE syndromes, whereas susceptibility loci at 2q34 and 13q31.3 preferentially predispose to either JME or GAE.
- Phenotype-genotype strategies applying narrowly-defined trait definitions in phenotypic homogeneous subsets of families improve the prospects to disentangle the genetic basis of common familial GGE syndromes.
Epilepsy Research (2010) 92, 1—29

REVIEW
Epileptogenic ion channel mutations: From bedside to bench and, hopefully, back again

Massimo Mantegazza,b,* Raffaella Rusconia,b Paolo Scalmanib, Giuliano Avanzinib, Silvana Franceschettib

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Modulatory Proteins Can Rescue a Trafficking Defective Epileptogenic Na\textsubscript{\textdollar} 1.1 Na\textsuperscript{+} Channel Mutant

Raffaella Rusconi,1* Paolo Scalmani,1* Rita Restano Cassulini,1 Giulia Giunti,1 Antonio Gambardella,3* Silvana Franceschetti,1 Grazia Annesi,4 Enzo Wanke,5 and Massimo Mantegazza1

Rescuing by interacting protein and membrane targeting

A Rescuable Folding Defective Na\textsubscript{\textdollar} 1.1 (SCN1A) Sodium Channel Mutant Causes GEFS+: Common Mechanism in Na\textsubscript{\textdollar} 1.1 Related Epilepsies?

Raffaella Rusconi 1, Romina Combi 2, Sandrine Cestele 1,3, Daniele Grioni 4, Silvana Franceschetti 1, Leda Dalprà 5, and Massimo Mantegazza 1,6,*
Glucose Transporter Type 1 (Glut1)
The expanding phenotype of GLUT1 deficiency syndrome

1) Epilepsy:
   - Absence epilepsy with early onset
   - IGE
   - Focal

2) Movement disorder: PED, writer's cramp, migraine with aura, ataxia, distonic tremor, dystonia, and choreoathetosis

3) Epilepsy & movement disorder

   Paroxysmal exercise induced dyskinesia with or without epilepsy (PED) (Weber et al, Suls et al 2008)

Early Onset Absence epilepsy (Suls et al 2009)
Myoclonic-Astatic Epilepsy (Muellen et al 2011)

De Vivo Syndrome (1991)
Carbohydrate-responsive sub-phenotype
Temporal lobe epilepsy: neuropathological and clinical correlations in 243 surgically treated patients.


We found tumours in 33% of patients, malformations of cortical development (MCD) in 45%, isolated HS in 14%, no lesion in 5% and less common lesions in 3%. HS was present in 8% of tumour cases and 70% of MCD. Statistical analysis of antecedents was significantly associated only with febrile seizures (FS). In 93 patients the antiepileptic drug therapy was withdrawn. Our findings show that MCD, which is significantly associated with HS, is the most common lesion in TLE and support the concept that an optimal outcome is obtained when mesial and neocortical structures are removed.
Sprouting is a more frequent phenomenon of epilepsy than cell loss

- Interneuron-specific inhibitory cell
- Synchronized dendritic inhibitory cells
- Pyramidal cells, no plasticity in dendrites
- Degenerating interneuron-specific inhibitory cell
- Asynchronous dendritic inhibitory cells
- Pyramidal dendrites with associative plasticity

Toth et al, 2010, Brain (Hungarian Academy of Sciences)
Vezzani, French, Bartfai, Baram
The role of inflammation in epilepsy
NATURE REVIEWS | NEUROLOGY
January 2011
Effects of XE991, retigabine, losigamone and ZD7288 on kainate-induced theta-like and gamma network oscillations in the rat hippocampus in vitro
Anne Boehlena,1, Alexandra Kunerta,1, Uwe Heinemann

Fig. 4 – Effects of retigabine on kainate-induced gamma frequency oscillations of areas CA3 and CA1 of rat

Fig. 6 – Effects of losigamone on kainate-induced gamma frequency oscillations of areas CA3 and CA1 of rat


Protocadherin 19 mutations in girls with infantile-onset epilepsy Neurology 2010;75:646-53

Identification of new mutations in neuronal migration disorders (NMD) causative genes and definition of the phenotypic spectrum associated to these mutations:

- In-frame deletion in FLNA causing familial periventricular heterotopia (PH) with skeletal dysplasia in males
- Genomic deletions/duplications in the LIS1 gene in lissencephaly
- Variable patterns of cortical malformations resulting from TUBB2B gene mutations

Identification of critical regions and genes for NMD:

- PH, mental retardation, and epilepsy associated with 5q14.3-q15 deletion
- Identification of a novel PH candidate gene in 6q27 through Array-CGH and RNAi approaches
The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission

*2Ingmar Blümcke, †Maria Thom, ‡Eleonora Aronica, §Dawna D. Armstrong, ¶Harry V. Vinters, #Andre Palmini, **Thomas S. Jacques, ††Giuliano Avanzini, †††A. James Barkovich, §§Giorgio Battaglia, ¶¶Albert Becker, ##Carlos Cepeda, ###Fernando Cendes, ####Nadia Colombo, ####Peter Crino, #####J. Helen Cross, ####Olivier Delalande, #######François Dubeau, ######John Duncan, #######Renzo Guerrini, ########Philippe Kahane, #######Gary Mathern, ######Imad Najm, #######Çiğdem Özkara, #######Charles Raybaud, #######Alfonso Repesa, ########Steven N. Roper, #######Noriko Salamon, ######Andreas Schulze-Bonhage, ######Laura Tassi,$$$$$$$$$$$$Annamaria Vezzani, and ††Roberto Spreatico
Layer-specific genes reveal a rudimentary laminar pattern in human nodular heterotopia Neurology 2009
The search for genetic markers of pharmacoresistance identified 5 genes:

- ATF6 (Activating transcription factor 6),
- KCNMB2 (Potassium large conductance calcium-activated channel, subfamily),
- AADACL2 (arylacetamide deacetylase-like 2)
- LOC201651 (arylacetamide deacetylase pseudogene)
- NETO1 (Neuropilin and toloid-like)

that could provide valuable clues to unravelling the mechanisms of antiepileptic drug resistance and to predicting response to pharmacological therapy.
INTEGRATION

• Synergy among different research groups
• Synergy among complementary approaches
• Synergy among basic and clinical research approaches
• Collaborative training programs (with exchange of fellows)

European epilepsy research area of excellence
CONTRIBUTION TO STANDARDS

• Classification of epilepsies
• Tissue collection
• Neuropathological diagnostic criteria
• Suitable animal models
Impact on Clinical Care and Practice

- The genetic study demonstrated an oligogenic predisposition of familial Generalized Epilepsies. Some microdeletions may play an important role.
- The effect of “rescue proteins” may explain the variability of genotype-phenotype relationship in genetic epilepsies.
- We have a new classification of cortical dysplasia.
- In temporal lobe epilepsy with hippocampal sclerosis the association of malformations of cortical development should be carefully investigated.
Impact on Clinical Care and Practice

• The role of inflammation in epileptogenesis is firmly established and ready to provide a basis for a therapeutic approach.
• Genes predisposing to resistance to antiepileptic drugs have been identified.
• Besides its scientific results the outcome of a project is measured by its capacity to provide the scientific community with innovative methods and persisting initiatives and to create a momentum which foster the development of epilepsy research.
Functional Genomics And Neurobiology Of Epilepsy: A Basis For New Therapeutic Strategies [Epicure]

Malta 2007