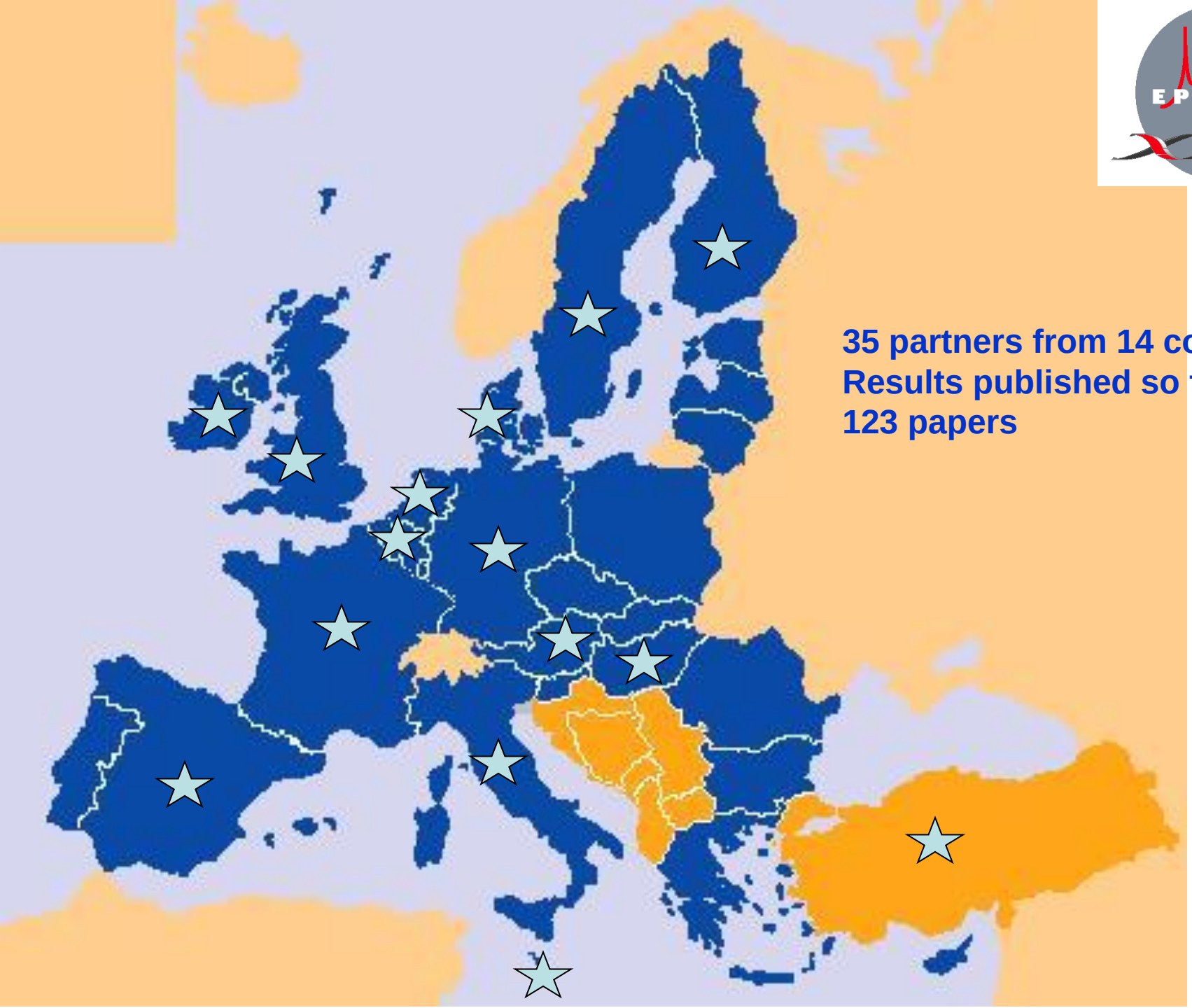
Functional Genomics and Neurobiology of Epilepsies
A Basis for New Therapeutic Strategies

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 123 papers

Functional Genomics And Neurobiology Of Epilepsy: A Basis For New Therapeutic Strategies [Epicure]

San Servolo
Venice 2006

nature genetics published online 11 January 2009

15q13.3 microdeletions increase risk of idiopathic generalized epilepsy

Ingo Helbig, Heather C Mefford, Andrew J Sharp, Michel Guipponi, Marco Fichera, Andre Franke, Hiltrud Muhle, Carolien de Kovel, Carl Baker, Sarah von Spiczak, Katherine L Kron, Ines Steinich, Ailing A Kleefu-Lie, Costin Leu, Verena Gaus, Bettina Schmitz, Karl M Klein, Philipp S Reif, Felix Rosenow, Yvonne Weber, Holger Lerche, Fritz Zimprich, Lydia Urak, Karoline Fuchs, Martha Feucht, Pierre Genton, Pierre Thomas, Frank Visscher, Gerrit-Jan de Haan, Rikke S Møller, Helle Hjalgrim, Daniela Luciano, Michael Wittig, Michael Nothnagel, Christian E Elger, Peter Nu¨rnberg, Corrado Romano, Alain Malafosse, Bobby P C Koeleman, Dick Lindhout, Ulrich Stephani, Stefan Schreiber, Evan E Eichler & Thomas Sander

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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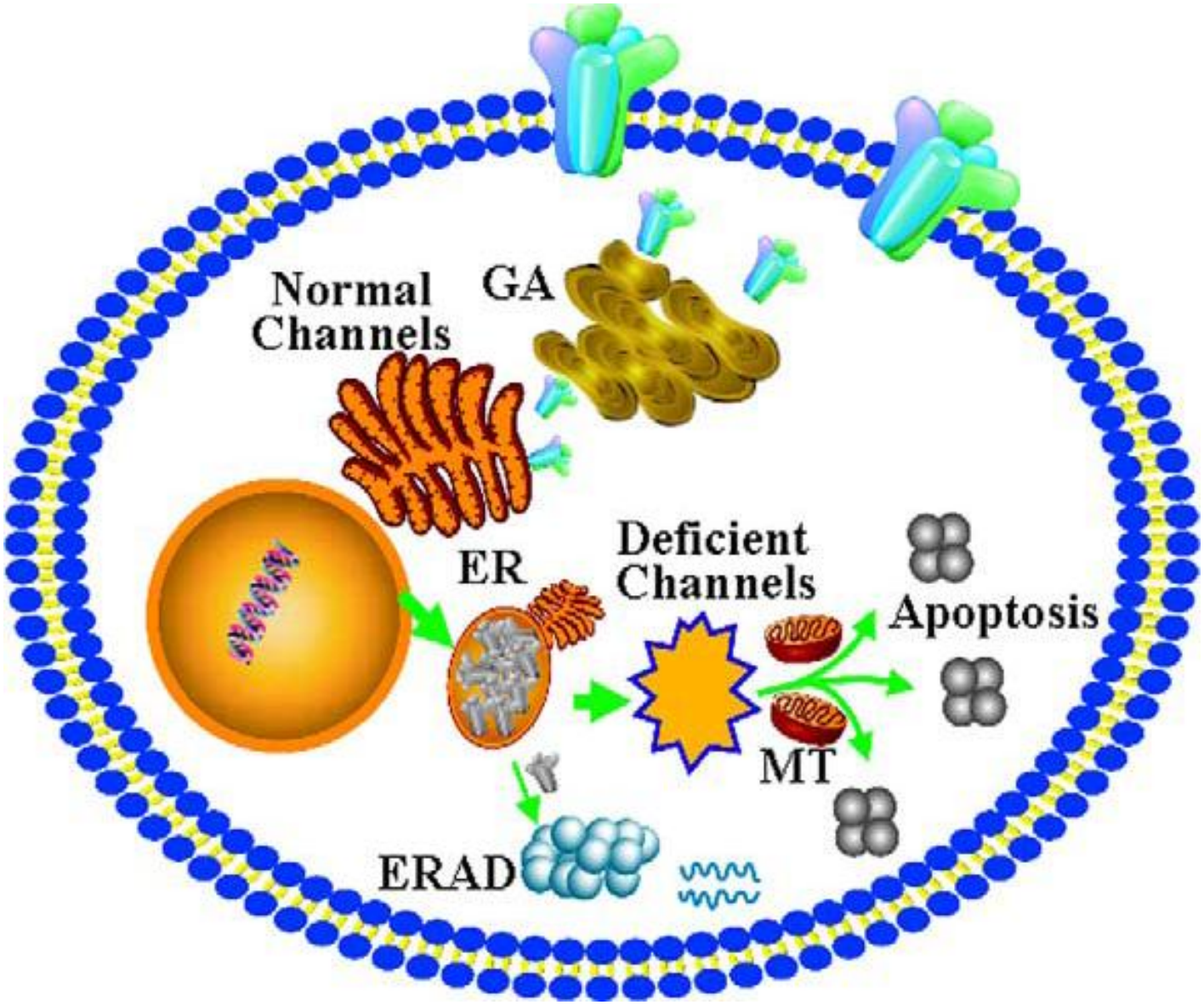
b *U.O. Neurofisiopatologia, Fondazione Istituto Neurologico Besta, Via Celoria 11, 20133 Milano, Italy*


Normal
Channels
GA
ER
Deficient
Channels
Apoptosis
MT
ERAD

The Journal of Neuroscience, October 10, 2007 • 27(41):11037–11046 • 11037

Neurobiology of Disease

Modulatory Proteins Can Rescue a Trafficking Defective Epileptogenic $Na_v1.1$ Na^+ Channel Mutant

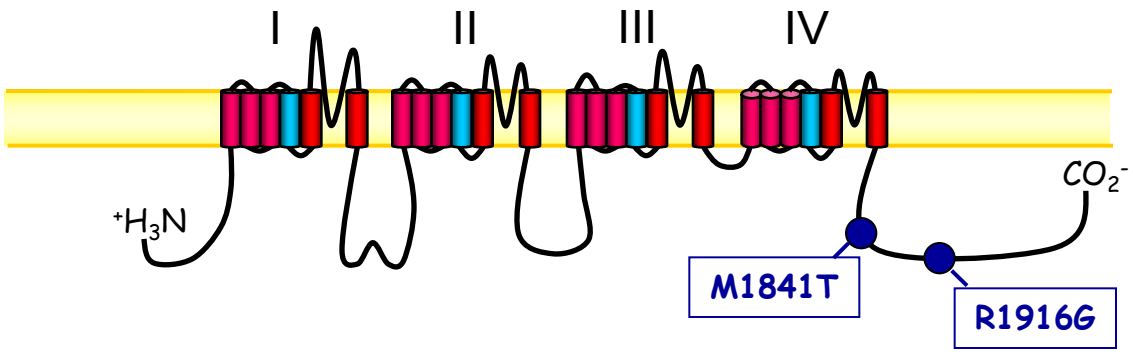
Raffaella Rusconi,[1]* Paolo Scalmani,[1]* Rita Restano Cassulini,[2] Giulia Giunti,[1] Antonio Gambardella,[3,4] Silvana Franceschetti,[1] Grazia Annesi,[4] Enzo Wanke,[2] and Massimo Mantegazza[1]

MUTATION IN BRIEF

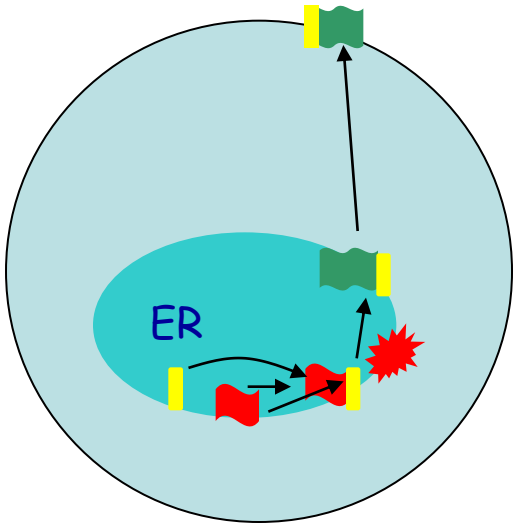
HUMAN MUTATION

A Rescuable Folding Defective $Na_v1.1$ (*SCN1A*) Sodium Channel Mutant Causes GEFS+: Common Mechanism in $Na_v1.1$ Related Epilepsies?

Raffaella Rusconi [1], Romina Combi [2], Sandrine Cestèle [1,3], Daniele Grioni [4], Silvana Franceschetti [1], Leda Dalprà [5], and Massimo Mantegazza [1,6,*]

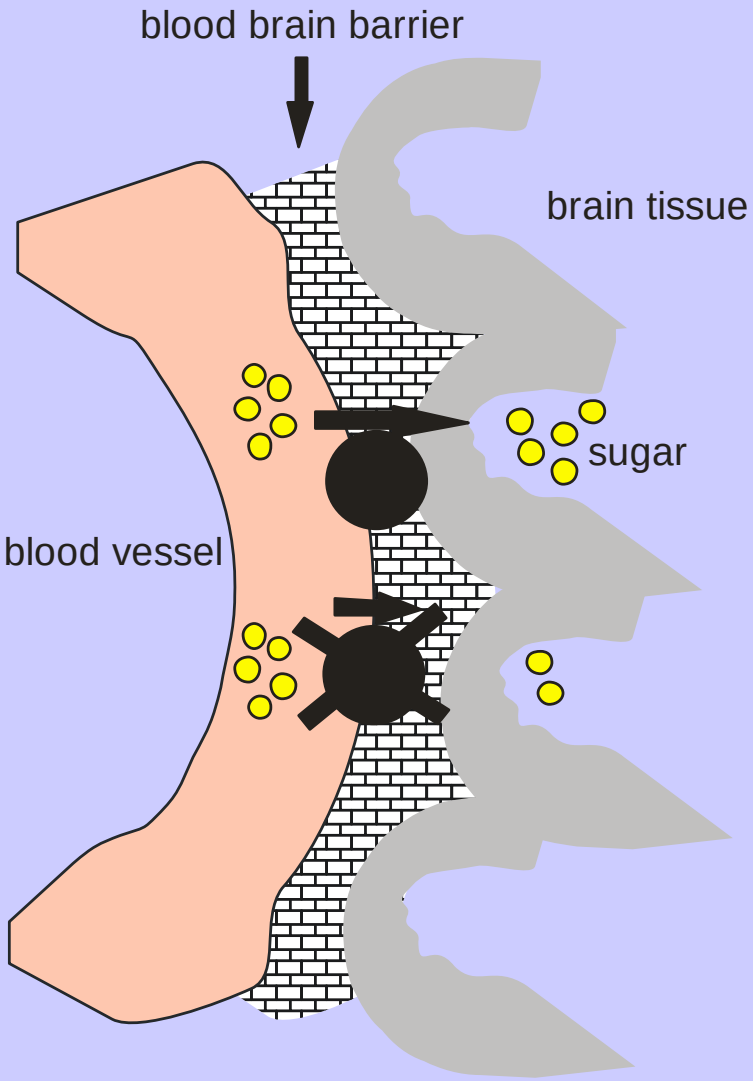


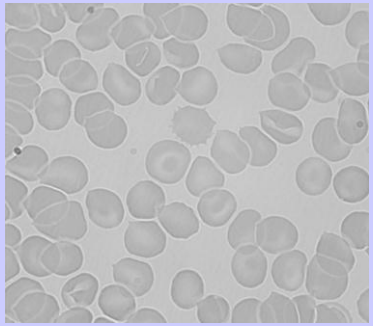
Rescuing by interacting protein and membrane targeting

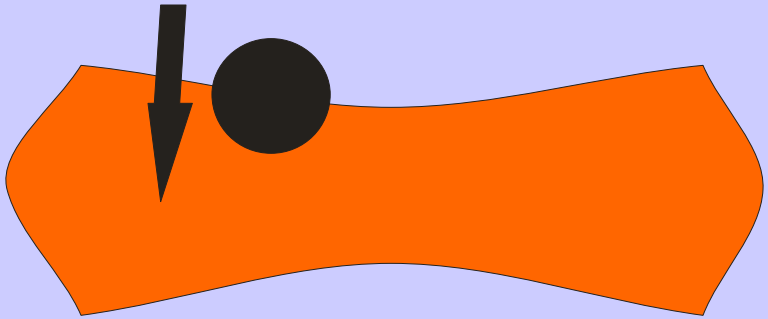


β subunit

Glucose Transporter Type 1 (Glut1)

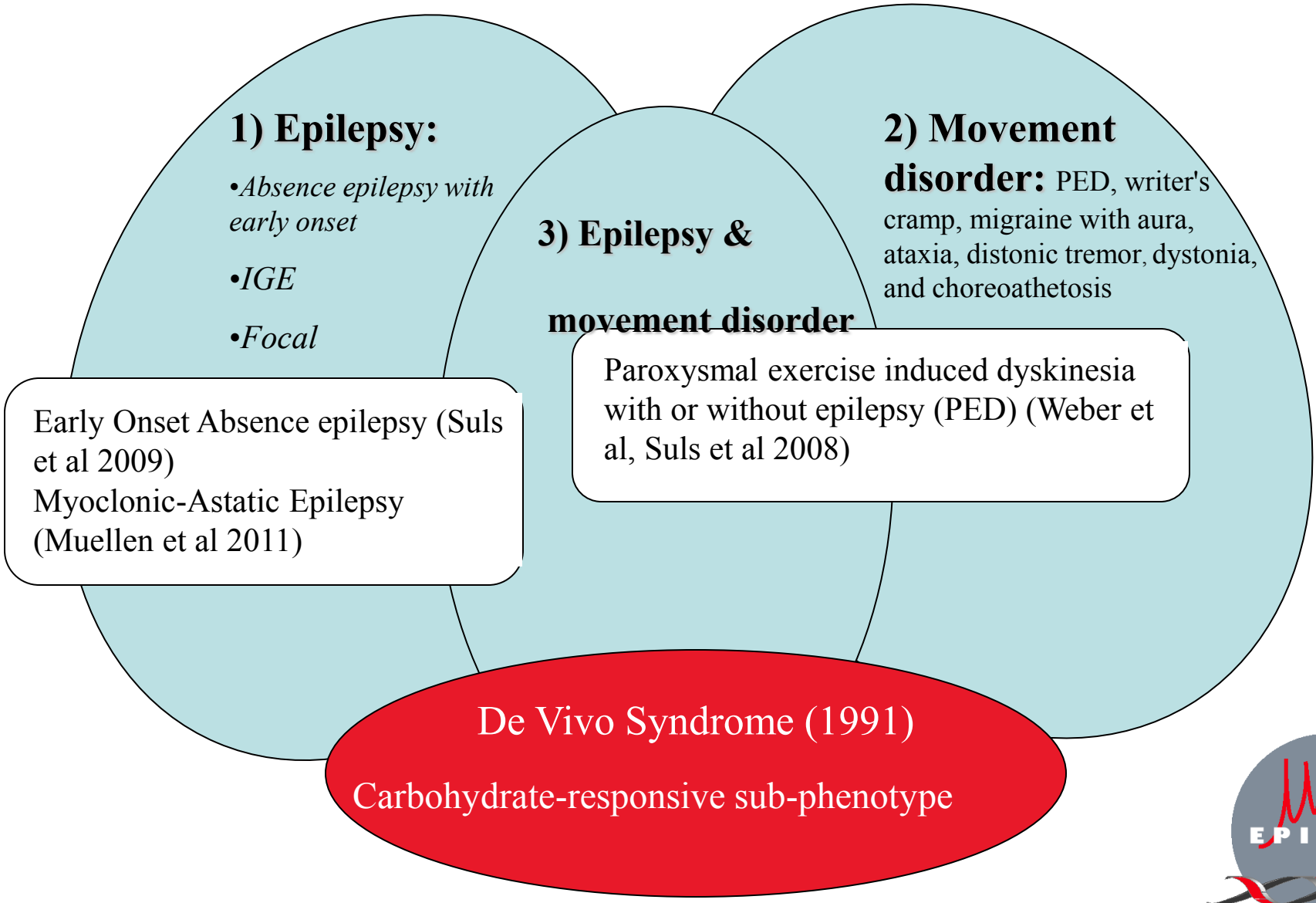






erythrozyte

The expanding phenotype of GLUT1 deficiency syndrome



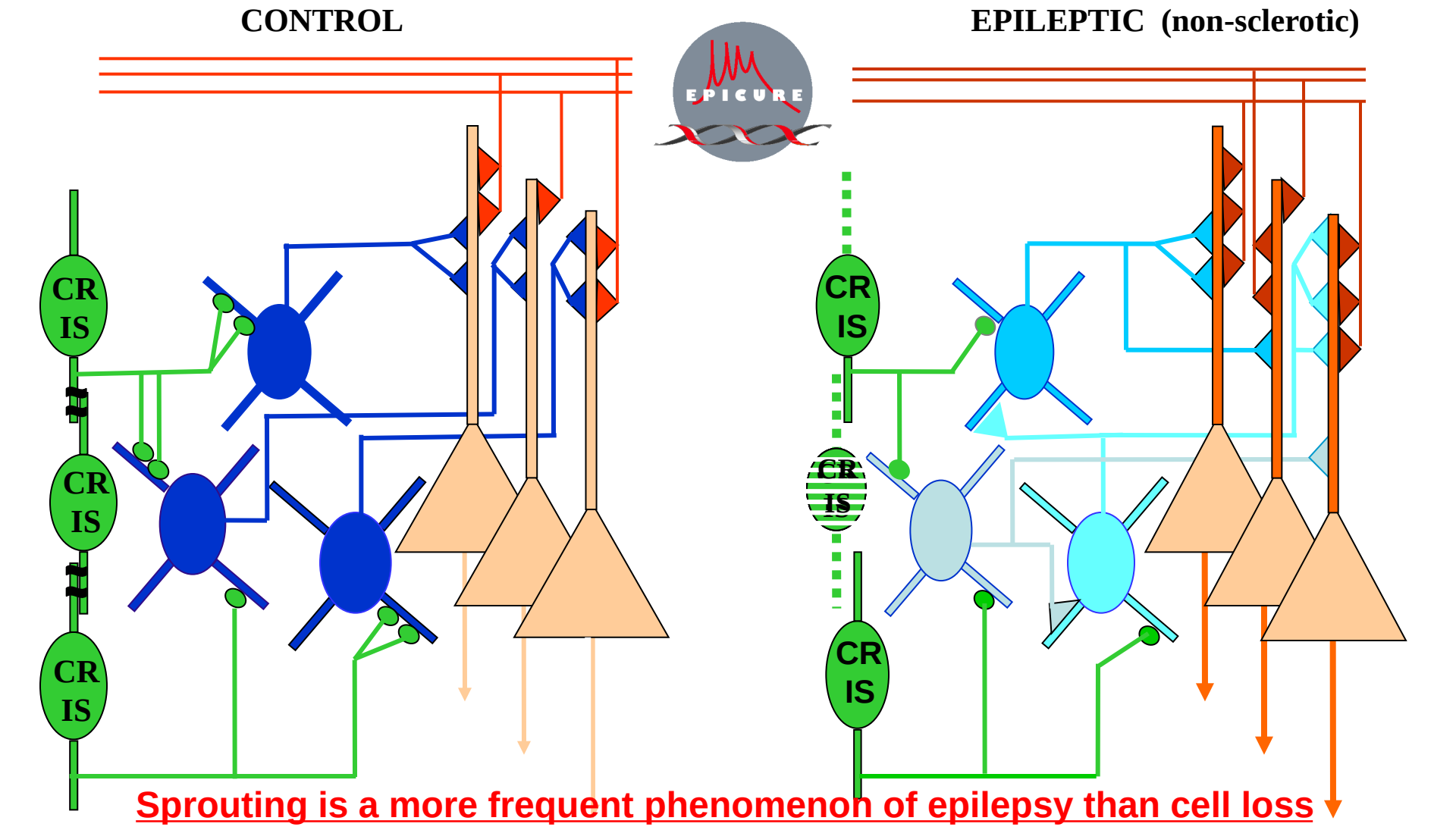
Epileptic Disord. 2009 Dec;11(4):281-92. Epub 2009 Nov 30.

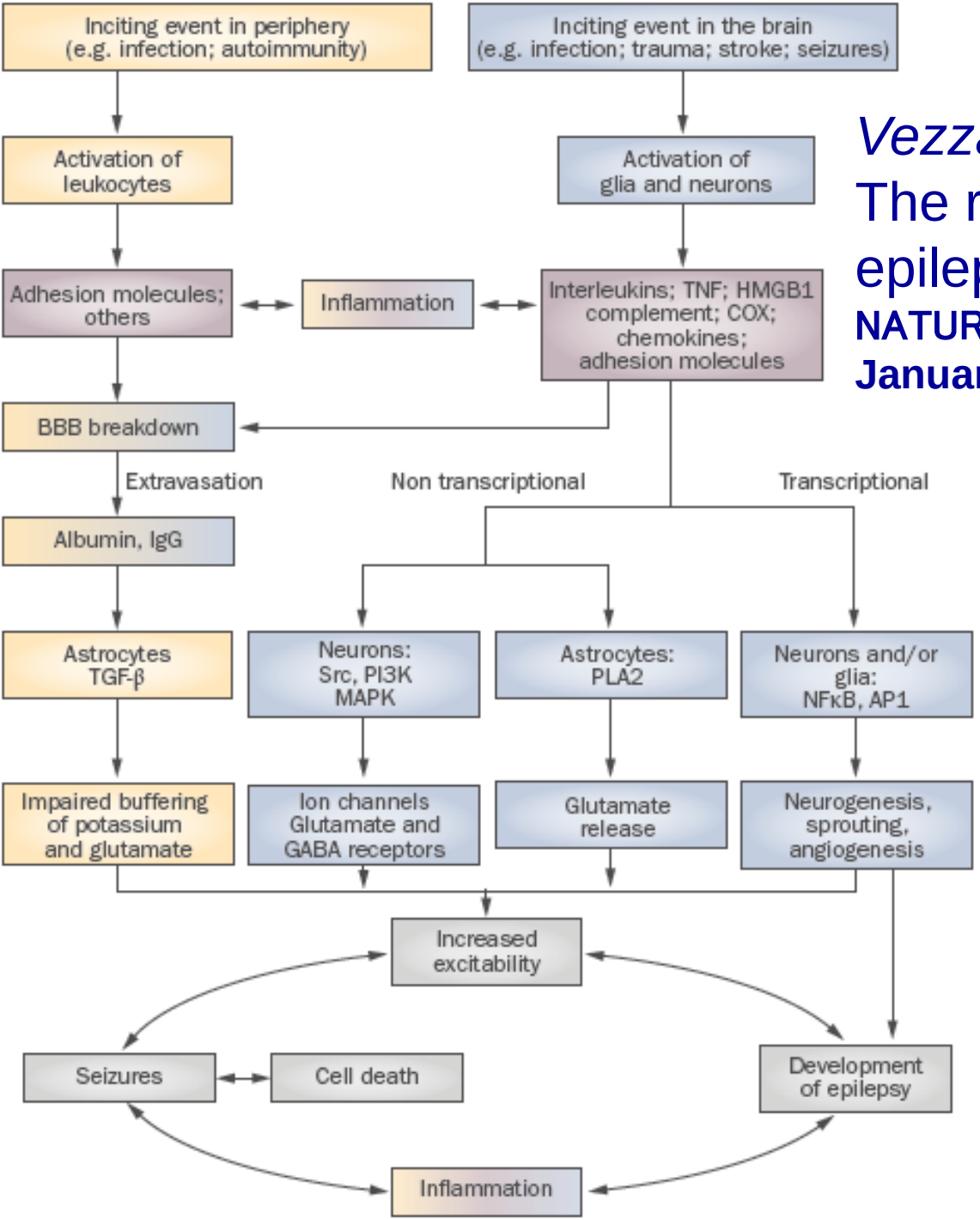
Temporal lobe epilepsy: neuropathological and clinical correlations in 243 surgically treated patients.

Tassi L, Meroni A, Deleo F, Villani F, Mai R, Russo GL, Colombo N, Avanzini G, Falcone C, Bramerio M, Citterio A, Garbelli R, Spreafico R.

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.

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

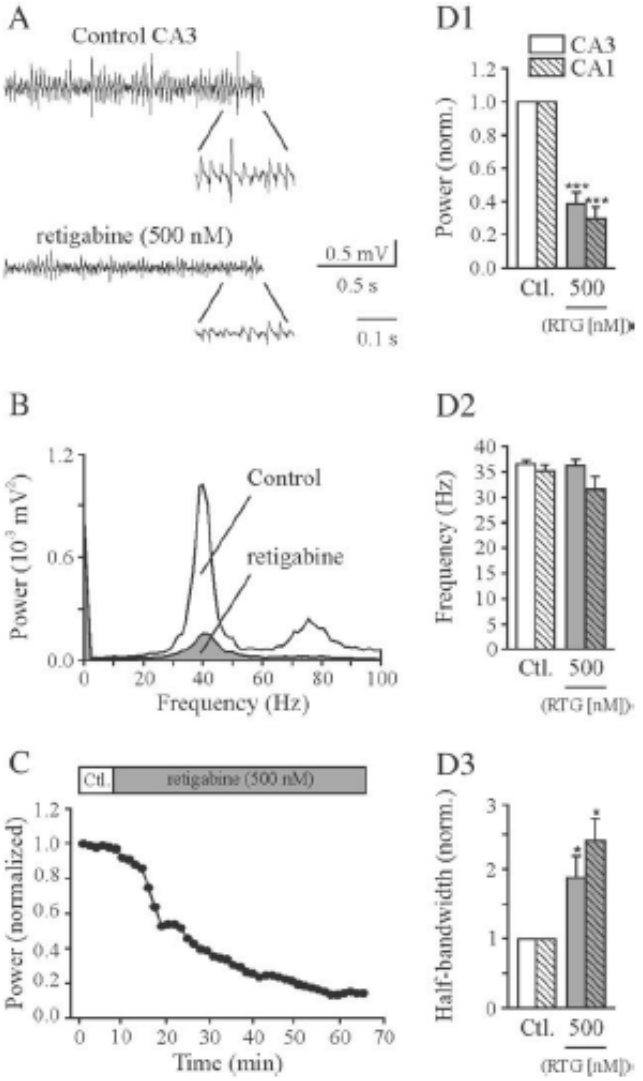


Fig. 4 – Effects of retigabine on kainate-induced gamma frequency oscillations of areas CA3 and CA1 of rat

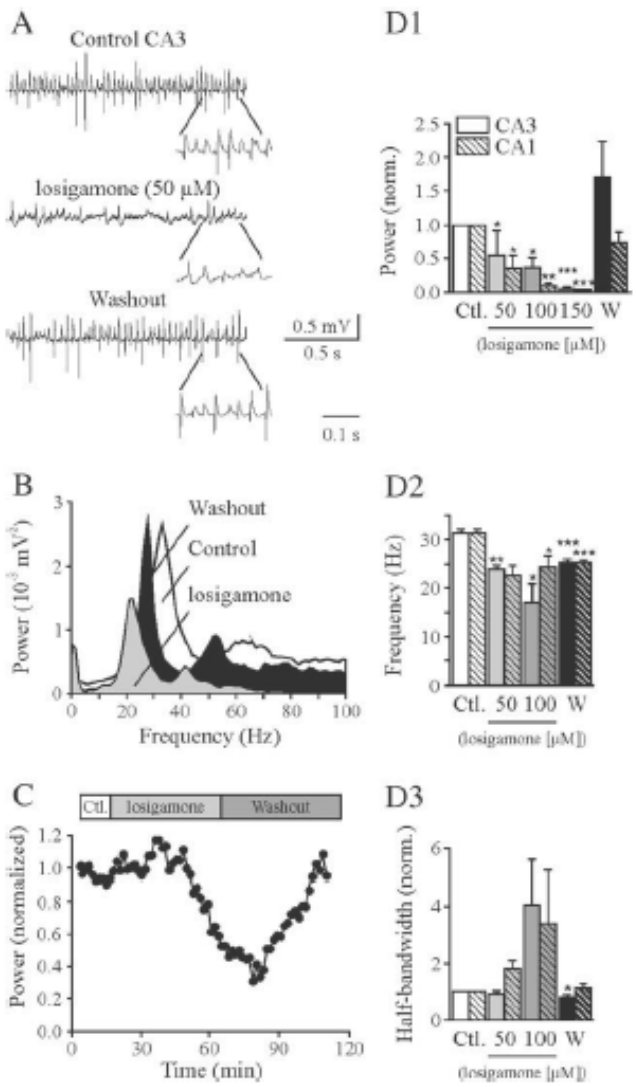


Fig. 6 – Effects of losigamone on kainate-induced gamma frequency oscillations of areas CA3 and CA1 of rat

Epilepsia, **(*):1–17, 2010
doi: 10.1111/j.1528-1167.2010.02777.x

SPECIAL REPORT

The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission[1]

*[2]Ingmar 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, ***[3]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 Represa, ‡‡‡‡‡Steven N. Roper, §§§§§Noriko Salamon, ¶¶¶¶¶Andreas Schulze-Bonhage, #####Laura Tassi, ******Annamaria Vezzani, and ††Roberto Spreafico

Cortical dysplasias of genetic origin

Elena Parrini, Davide Mei, Valerio Conti, Paola Sgadò, Carla Marini and Renzo Guerrini

The malformations of cortical development (MCD) represent a major cause of developmental disabilities, severe epilepsy, and reproductive disadvantage. Genes that have been associated with MCD are mainly involved in cell proliferation and specification, neuronal migration and late cortical organization.

Lissencephaly-pachygyria-subcortical band heterotopias (SBH) are diffuse neuronal migration disorders associated with abnormalities of the *LIS1*, *DCX*, *ARX*, *RELN*, and *TUBA1A* genes. *LIS1*-related lissencephaly is more severe in the posterior brain regions, whereas *DCX*-related lissencephaly is more severe in the anterior brain. Most cases of classical lissencephaly are caused by deletions or mutations of *LIS1*, whereas most cases of SBH are due to mutations of *DCX*. Posterior SBH casue by mosaic mutations of *LIS1* has also been described. X-linked lissencephaly with agenesis of the corpus callosum and ambiguous genitalia in males is associated with mutations of the *ARX* gene, whereas autosomal recessive lissencephaly with cerebellar hypoplasia has been associated with mutations of the *RELN* gene. The clinical and anatomical spectrum of *TUBA1A*-related lissencephaly is still to be defined but appears to be broad.

Periventricular heterotopia is genetically heterogeneous. *FLNA* mutations have been reported in all familial X-linked cases and in about 25 per cent of sporadic cases. A rare bilateral recessive form with microcephaly is caused by mutations of the *ARFGEF2* gene. Several different chromosomal rearrangements have been described in patients with periventricular heterotopia but the causative genes remain unknown.

Polymicrogyria is a common cortical malformation and is associated with numerous patterns and syndromes and with mutations in many genes, of which only a few have been identified. Among syndromes featuring polymicrogyria, bilateral perisylvian polymicrogyria (BPP) shows genetic heterogeneity, including linkage to chromosome Xq28 in some pedigrees, autosomal dominant or recessive inheritance in others, and an association with chromosome 22q11.2 deletion in some patients. Mutations of the *SRPX2* gene have been related to BPP, but the role of this gene has still to be confirmed. Recessive bilateral frontoparietal polymicrogyria has been associated with mutations of the *GPR56* gene.

Layer-specific genes reveal a rudimentary laminar pattern in human nodular heterotopia

R. Garbelli, L. Rossini, Moroni, A. Watakabe, T. Yamamori, L. Tassi, M. Bramerio, Russo, C. Frassoni, R. Spreafico,

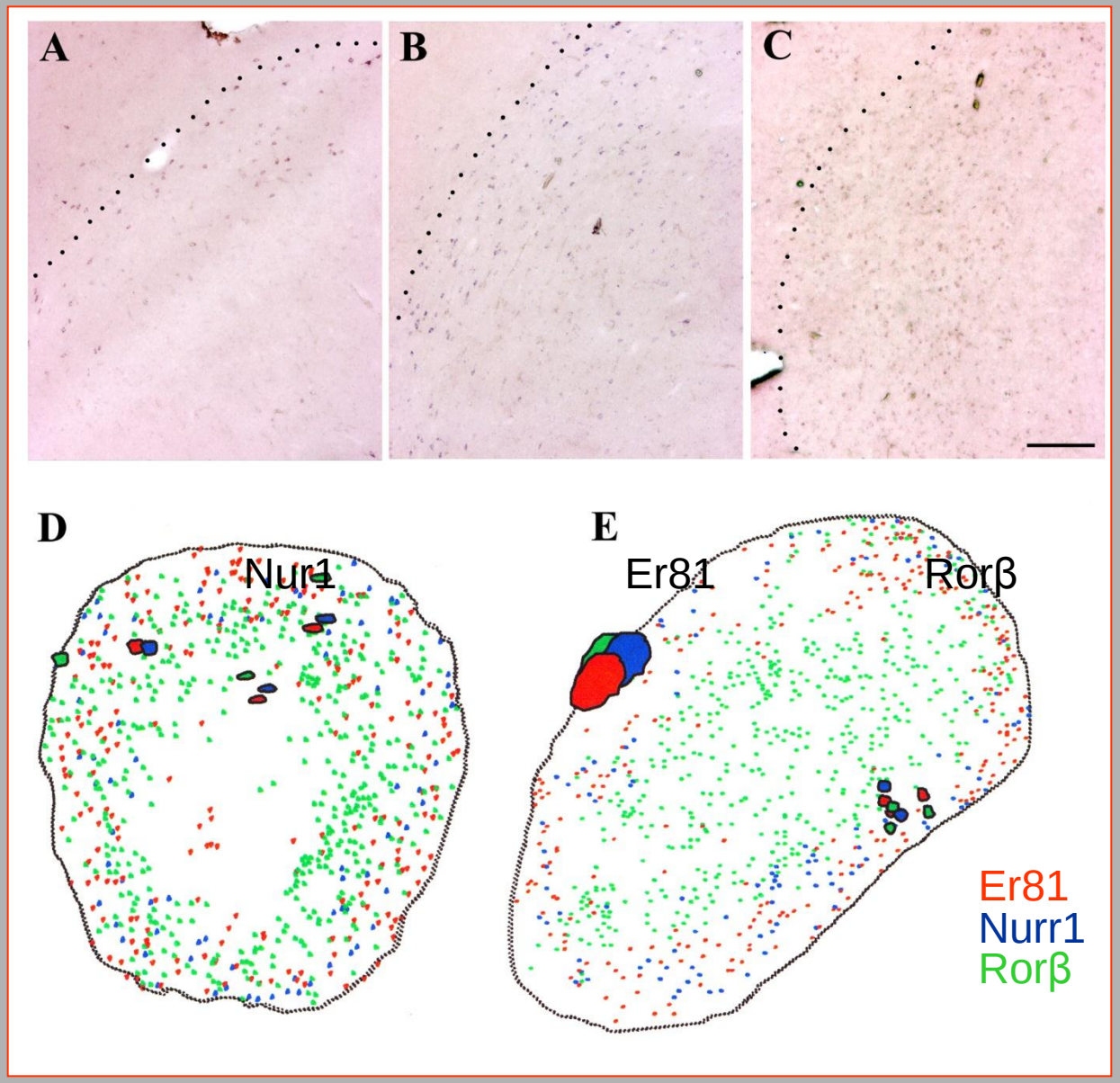
ABSTRACT

Objective: To define distinctive features of nodular heterotopia in specimens derived from drug-resistant patients with epilepsy by evaluating mRNA expression of three different layer-specific markers: Rorβ, Er81, and Nurr1.

Methods: We analyzed the expression profile of these genes, recognized as markers mainly expressed in layer IV for Rorβ, in layer V for Er81, and in layer VI for Nurr1, in surgical samples from 14 epileptic patients, using in situ hybridization. Six patients had subcortical nodular heterotopia and 8 patients were controls. The intrinsic organization of nodular formations and of the overlaying neocortex was assessed.

Results: In all patients, the 3 selected genes showed high cortical laminar specificity. In subcortical nodular heterotopia, the different gene expression profiles revealed a rudimentary laminar organization of the nodules. In the overlaying cortex, fewer cells expressed the 3 genes in the appropriate specific layer as compared to controls.

Conclusions: These data provide new insights into possible ontogenetic mechanisms of nodular heterotopia formation and show the potential role of layer-specific markers to elucidate the neuropathology of malformations of cortical development. *Neurology*®



From Garbelli…….Spreafico Layer-specific genes reveal a rudimentary laminar pattern in human nodular heterotopia Neurology 2009

THE PHARMACOGENOMICS OF FOCAL EPILEPSIES

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 tolloid-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 appoaches
- 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

CONCLUSIONS

- Besides the scientific results the EPICURE project ends up with some “products” that will be widely beneficial for the scientific community such as innovative **methods and techniques** that had been developed during the project and a **general tissue brain bank** that has been established in Erlangen
- EPICURE substantially contributed in establishing a network of excellence in epilepsy research and created a momentum which will have an important impact in fostering future development of epilepsy research in Europe.
- We are glad and proud for being involved in it.

Functional Genomics And Neurobiology Of Epilepsy: A Basis For New Therapeutic Strategies [Epicure]

Malta 2007