GENETICA
(parte 2)

Biomarcatori Genetici nelle Epilessie Idiopatiche

Antonio Gambardella

Istituto di Neurologia, Dipartimento Scienze Mediche e Chirurgiche, *UMG* Catanzaro
Istituto di Bioimmagini e Fisiologia Molecolare Cnr, Segrate (MI) – U.O.S. Germaneto (CZ)

Epilessie & *"Biomarcatori"* Genetici

"Outline":

- "Epilessie Mendeliane"
- Canalopatie ed oltre …
- Epilessie complesse
- Identificazione di *"Biomarcatori"* Genetici

Biomarcatore Genetico

- Definizione -

Si definisce **biomarcatore genetico** ogni *variante genetica (mutazione o polimorfismo)* correlata con l'insorgenza, lo sviluppo, la prognosi e/o la risposta alla terapia (farmacoresistenza) di una determinata malattia.

Epilepsia
2013; 54 Suppl4:61-9.

Epilepsy biomarkers.

Engel J Jr, Pitkänen A, Loeb JA, Dudek FE, Bertram EH 3rd, Cole AJ, Moshé SL, Wiebe S, Jensen FE, Mody I, Nehlig A, Vezzani A.

Epileptogenicity

- Refers to the **presence and severity** of an epilepsy condition
- ***Goal***: To identify persistent, dynamic disturbances that indicate the presence of epileptogenicity and its severity
- **Tool**: Genetic, molecular, physiologic, and anatomic understanding of the epileptogenic abnormality

Epileptogenesis

- Refers to the **development and progression** of an epilepsy condition
- ***Goal***: To identify persistent, dynamic disturbances that predict epileptogenesis
- **Tool**: Tracking the processes identified as underlying epileptogenesis

Genes for Monogenic Epileptic *Channelopathies*

Gene	Syndrome	Year of discovery
CHRNA4	ADNFLE	1995
KCNQ2	BFNS	1998
KCNQ3	BFNS	1998
SCN1B	GEFS^{+}	1998
SCN1A	GEFS^{+}/SMEI	2000/(01)
CHRNB2	ADNFLE	2000
GABRG2	CAE/FS/GEFS^{+}	2001
SCN2A	GEFS^{+}/BFNIS	2001/02
GABRA1	ADJME, CAE	2002/06
CLCN2	IGE	2003
CHRNA2	ADNFLE	2006
HCN2	IGE	2011
KCNT1	ADNFLE/MMPSI	2012
GRIN2A (NMDAR)	BECTS ➡ LKS/ESES	2013

Non Ion-Channel Genes for Monogenic Idiopathic Epilepsies

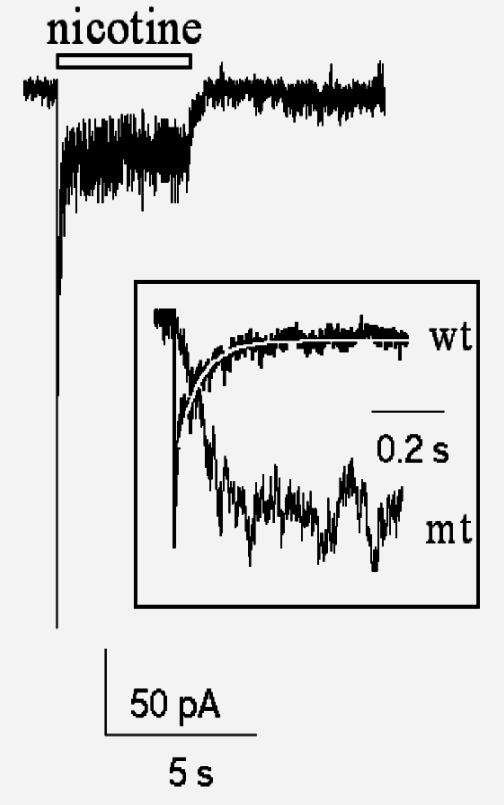
Gene	Syndrome	Year of discovery
LGI1	ADLTLE	2002
EFHC1	JME	2004
SLC2A1	Early onset AE, IGE, GLUT1 deficiency	2009
PRRT2	BFIS/PKD	2011-'12
DEPDC5	FFEVF	2013
DEPDC5	FFEVF/Focal Epilepsies	2013
STX1B	Fever-associated epilepsy syndromes	2014

nature genetics
2000; 26(3):275-6

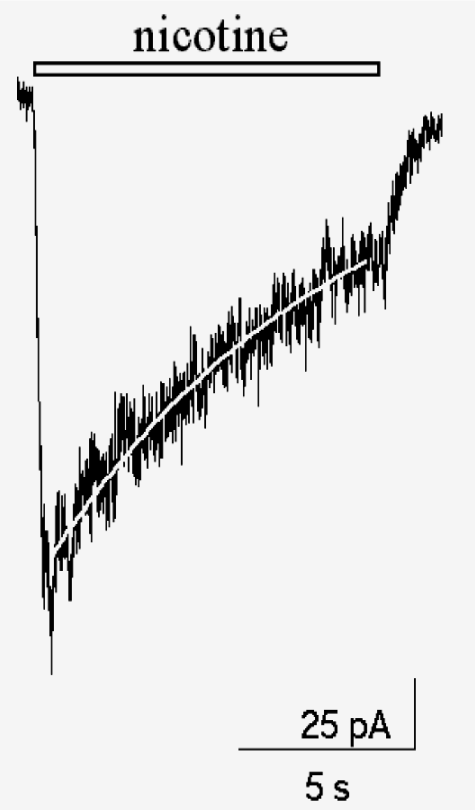
The nicotinic Receptor ß2 subunit is mutant in nocturnal frontal lobe epilepsy

De Fusco M, Becchetti A, Patrignani A, Annesi G, Gambardella A, Quattrone A, Ballabio A, Wanke E, Casari G.

Electrophysiology of **wt** and **mutant** nicotinic receptors



wt



mutant

The NEW ENGLAND JOURNAL of MEDICINE

2013; 369:1502-1511

Clinical Whole-Exome Sequencing for the Diagnosis of Mendelian Disorders

Yang Y, Muzny DM, Reid JG, Bainbridge MN, Willis A, Ward PA, Braxton A, Beuten J, Xia F, Niu Z, Hardison M, Person R, Bekheirnia MR, Leduc MS, Kirby A, Pham P, Scull J, Wang M, Ding Y, Plon SE, Lupski JR, Beaudet AL, Gibbs RA, Eng CM.

Whole-exome sequencing identified the underlying genetic defect in **25%** of consecutive patients referred for evaluation of a possible genetic condition.

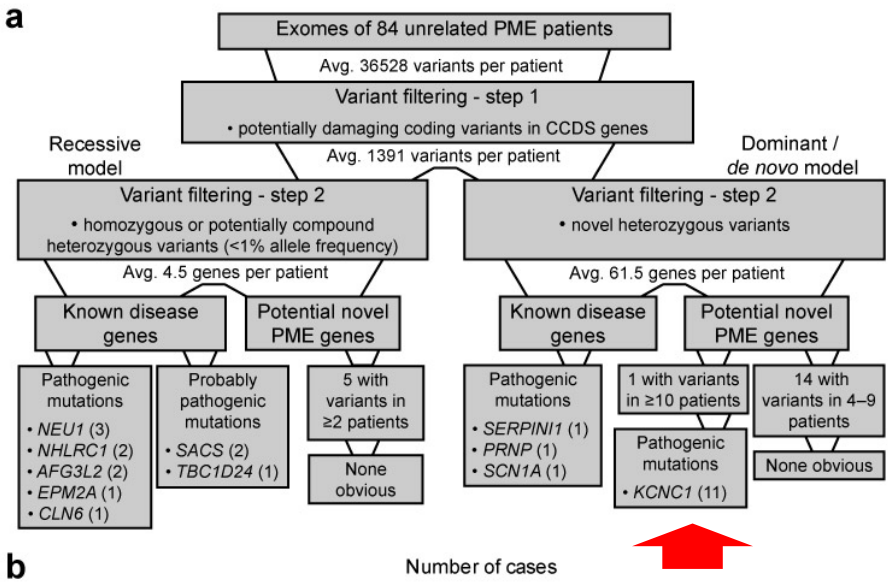
Table 5. Inheritance Pattern and Medical Presentation of Patients with Established Molecular Diagnosis.

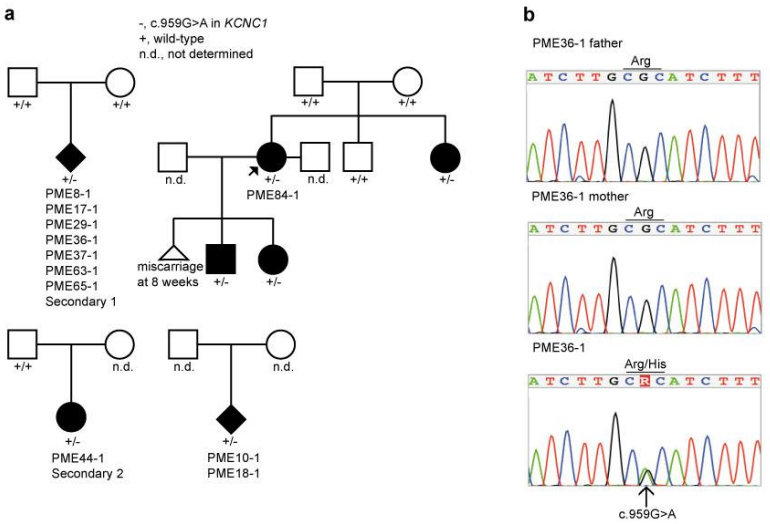
Primary Phenotype Category	No. of Patients Tested	Positive Diagnosis					Rate of Positive Diagnosis (95% CI)
		Autosomal Dominant Trait	Autosomal Recessive Trait	X-Linked Trait	Two Traits	Total	
		number of patients					*percent*
Neurologic disorder	60	9	6	4	1	20	33 (23–46)
Neurologic disorder and other organ-system disorder	140	19	4	5	3	31	22 (16–30)
Specific neurologic disorder	13	1	3	0	0	4	31 (13–58)
Non-neurologic disorder	37	4	3	0	0	7	19 (9–34)
Total	250	33	16	9	4	62	25 (20–31)

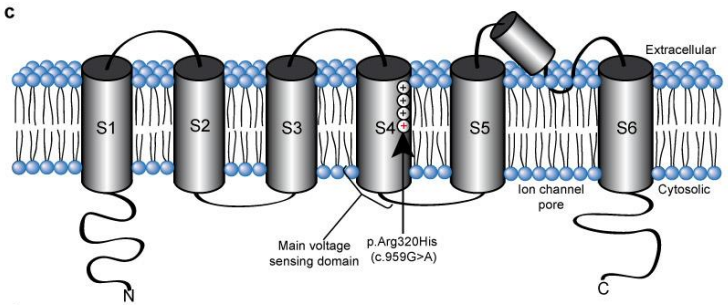
nature genetics
2015;47:39-46

A recurrent *de novo* mutation in KCNC1 is a major cause of progressive myoclonus epilepsy

Muona M, Berkovic S, Dibbens L, Oliver K, Maljevic S, Bayly M, Joensuu T, Canafoglia L, Franceschetti S, Michelucci R, Markkinen S, Heron S, Hildebrand M, Andermann E, Andermann F , Gambardella A , Tinuper P, Licchetta L, Scheffer I, Criscuolo C, Filla A, Ferlazzo E, Ahmad J, Ahmad A, Baykan B, Said E, Topçu M, Riguzzi P, King M, Ozkara C, Andrade D, Engelsen B, Crespel A, Lindenau M, Lohmann E, Saletti V, Massano J, Privitera M, Espay A, Kauffmann B, Duchowny M, Steensbjerre Moller S, Straussberg S, Afawi Z, Ben-Zeev B, Samocha K, Daly M, Petrou S, Lerche H, Palotie A.

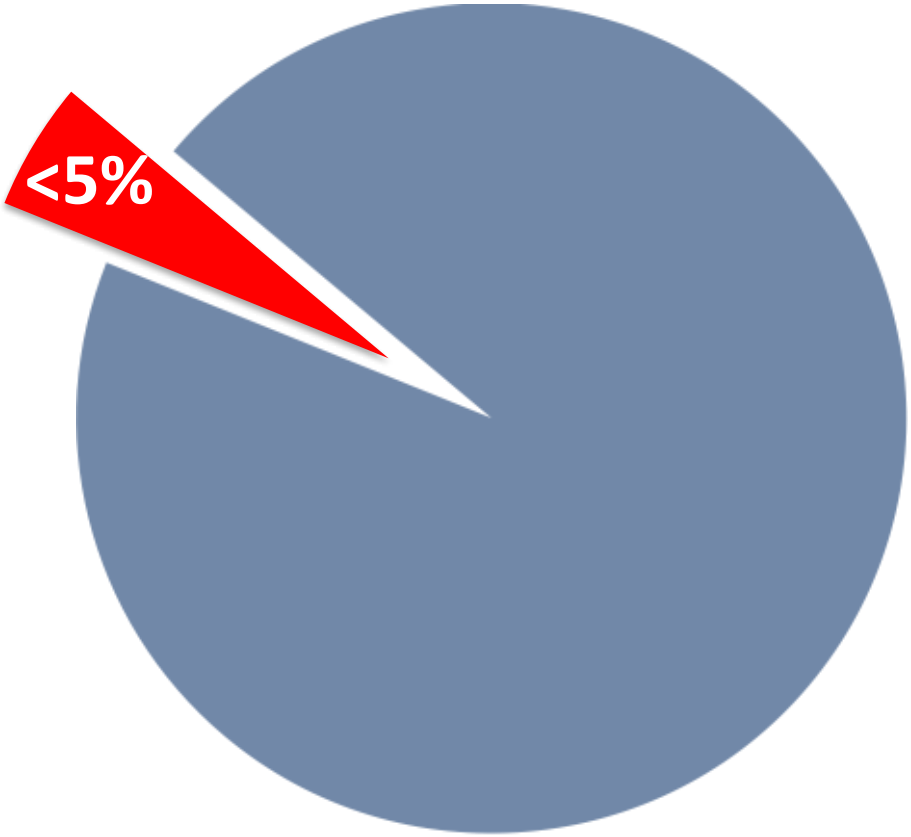


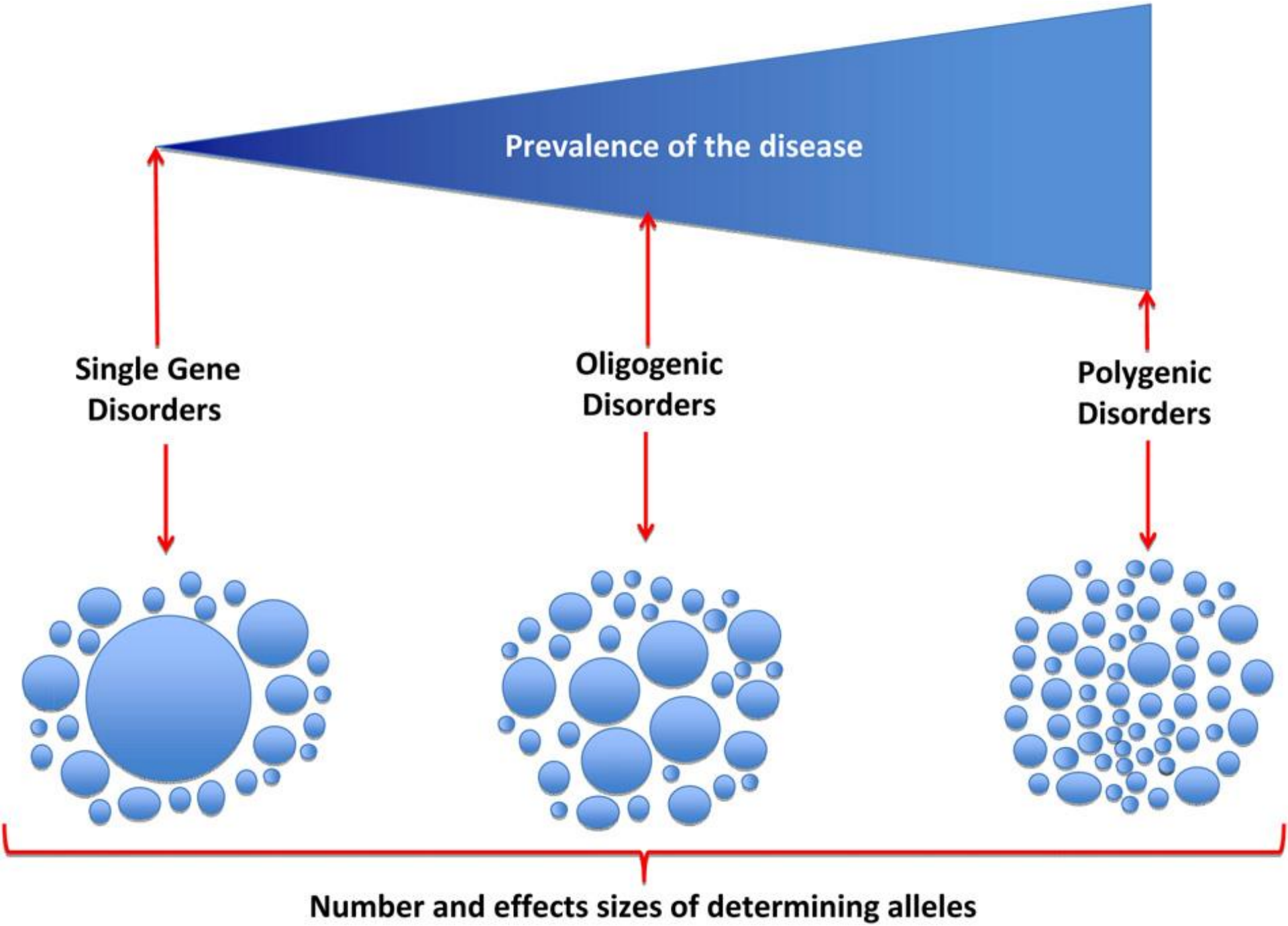




Prevalence of Epilepsies & Genetics

Monogenic epilepsies

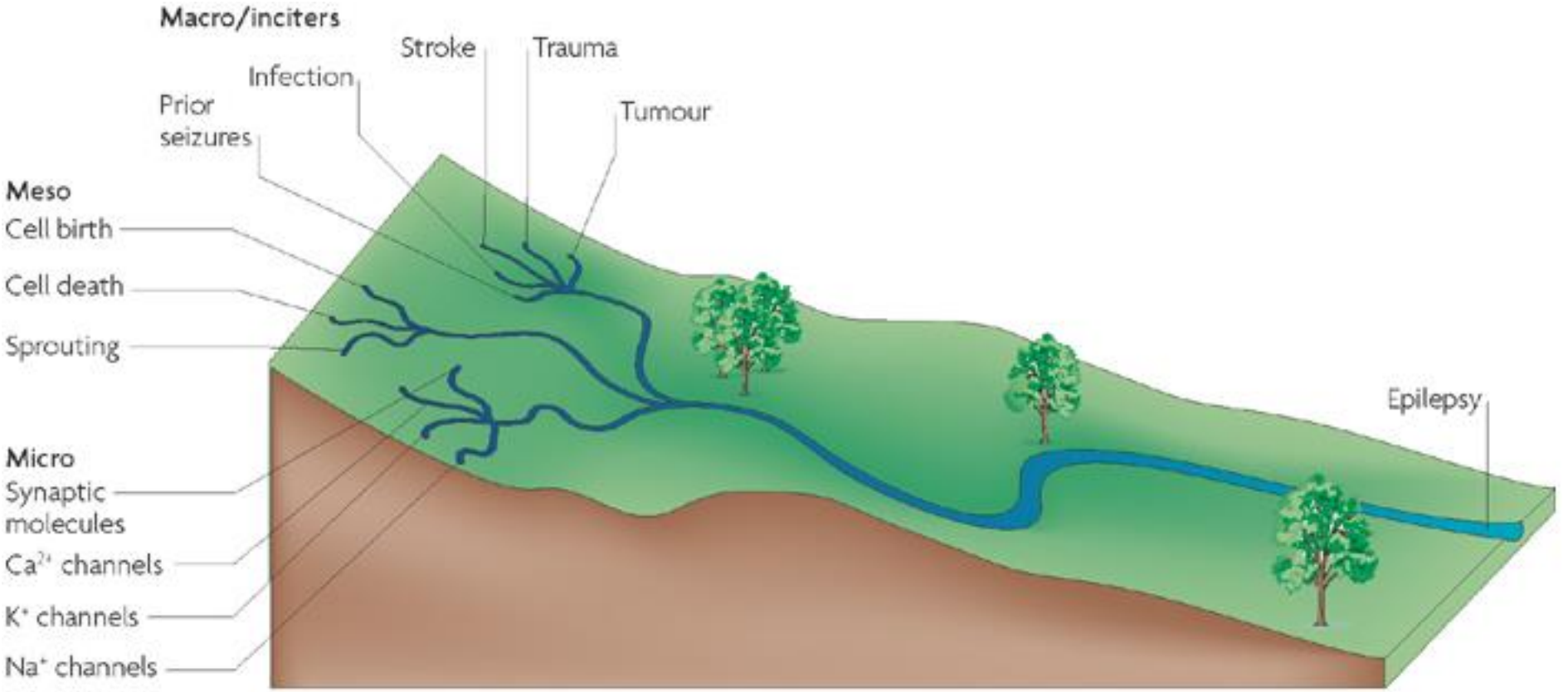



Prevalence of the disease
Single Gene Disorders
Oligogenic Disorders
Polygenic Disorders
Number and effects sizes of determining alleles

Sporadic epilepsy

Polygenic/multifactorial disorder

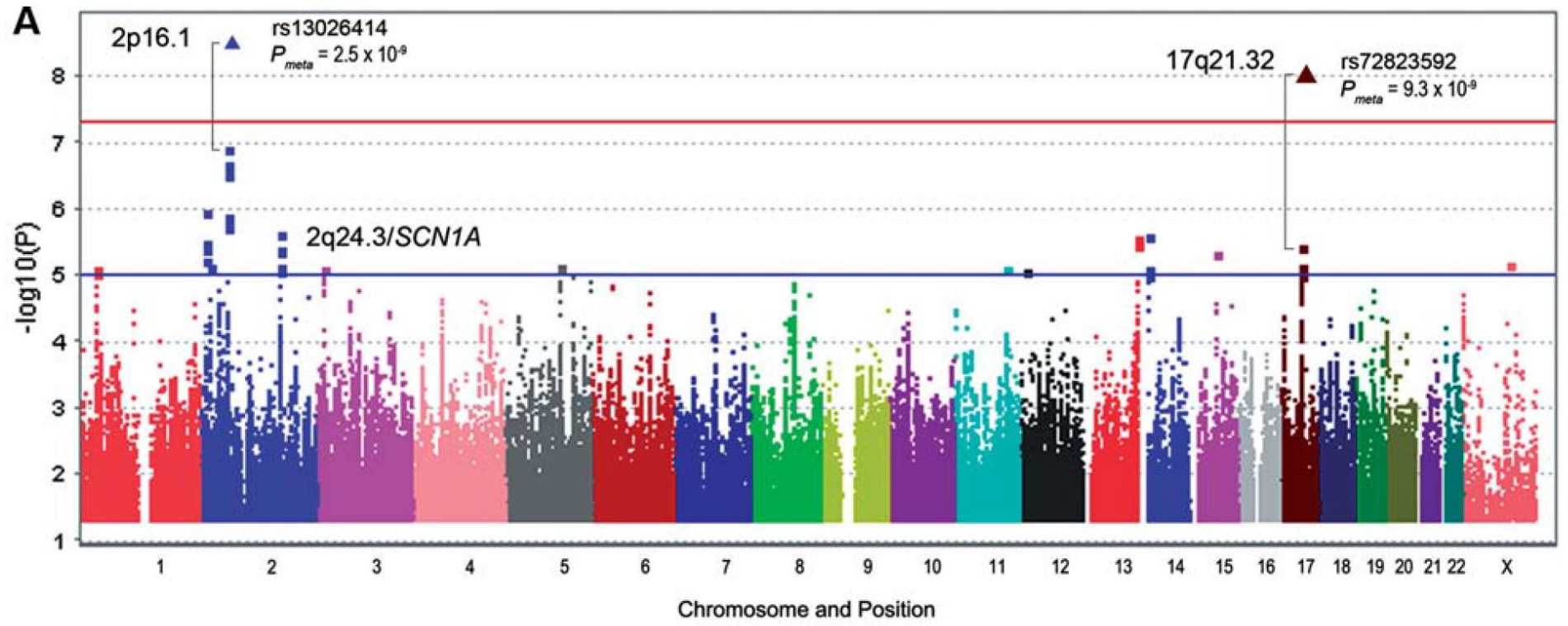
The river of epilepsy (Lennox, 1950)



Human Molecular Genetics
2012;21(24):5359-72

Genome-wide association analysis of genetic generalized epilepsies implicates susceptibility loci at 1q43, 2p16.1, 2q22.3 and 17q21.32.

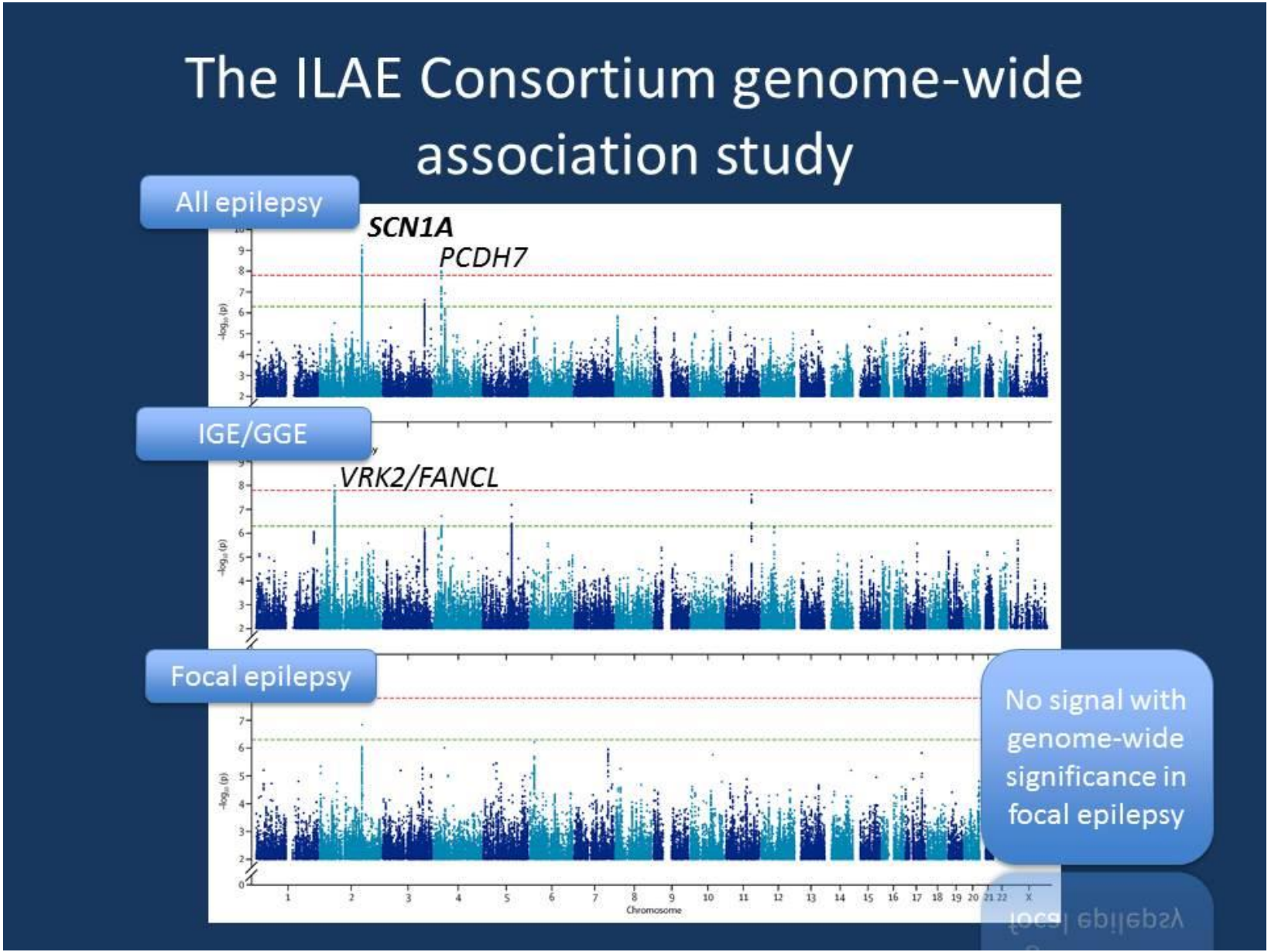
EPICURE Consortium; EMINet Consortium, Steffens M, Leu C, Ruppert AK, Zara F, Striano P, Robbiano A, Capovilla G, Tinuper P, Gambardella A, Bianchi A, La Neve A, Crichiutti G, de Kovel CG, Kasteleijn-Nolst Trenité D, de Haan GJ, Lindhout D, Gaus V, Schmitz B, Janz D, Weber YG, Becker F, et al.



THE LANCET Neurology
2014; 13(9): 893-903

Genetic determinants of common epilepsies: a meta-analysis of genome-wide association studies

International League Against Epilepsy Consortium on Complex Epilepsies

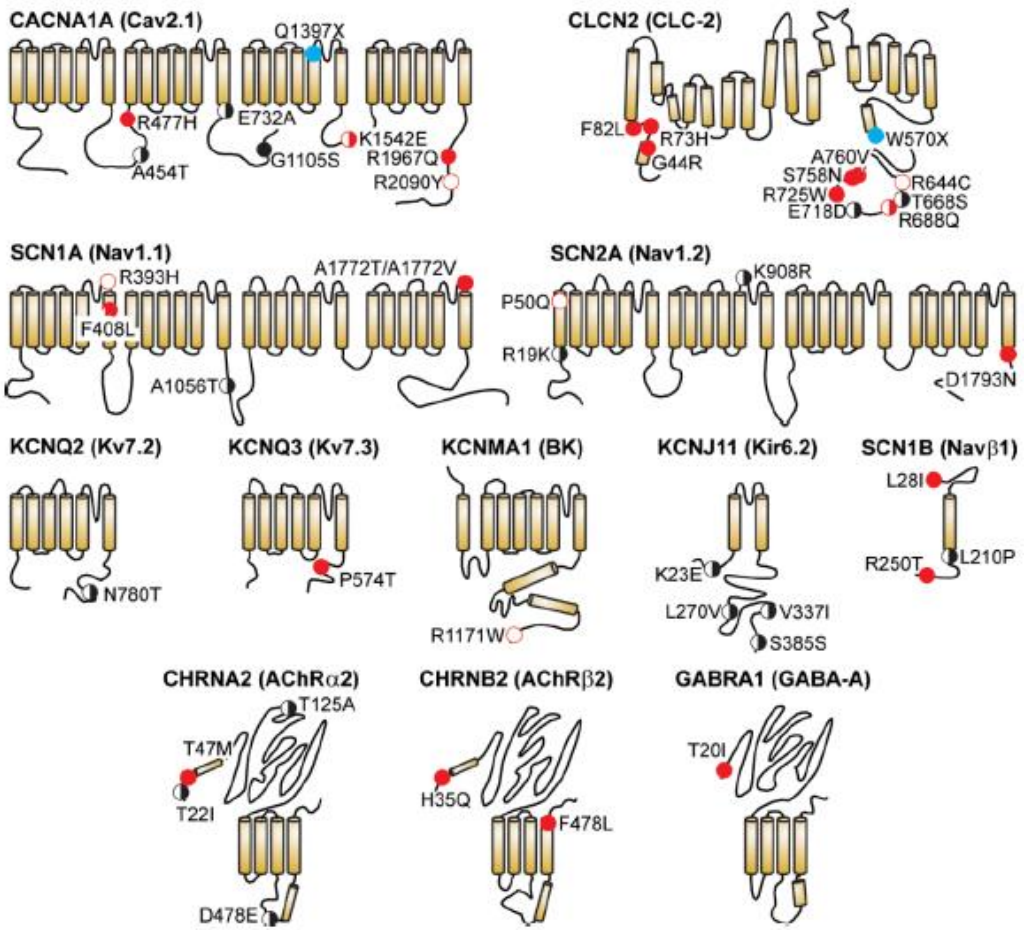


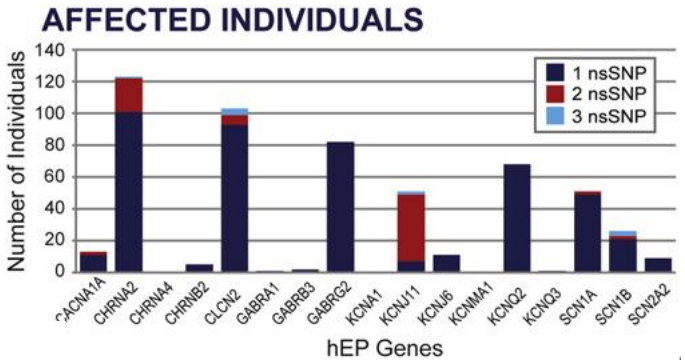
Cell

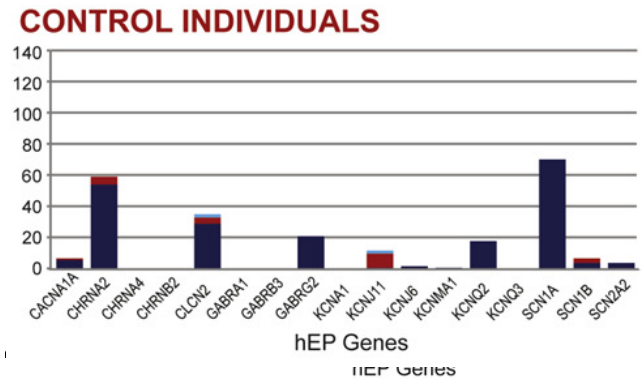
2011; 145: 1036–48

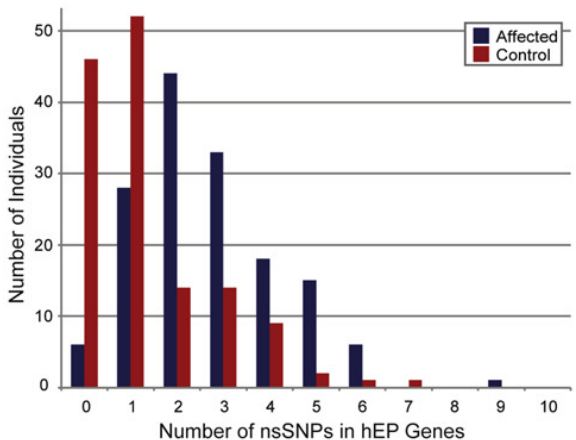
Exome sequencing of ion channel genes reveals complex profiles confounding personal risk assessment in epilepsy.

Klassen T, Davis C, Goldman A, Burgess D, Chen T, Wheeler D, McPherson J, Bourquin T, Lewis L, Villasana D, Morgan M, Muzny D, Gibbs R, Noebels J.





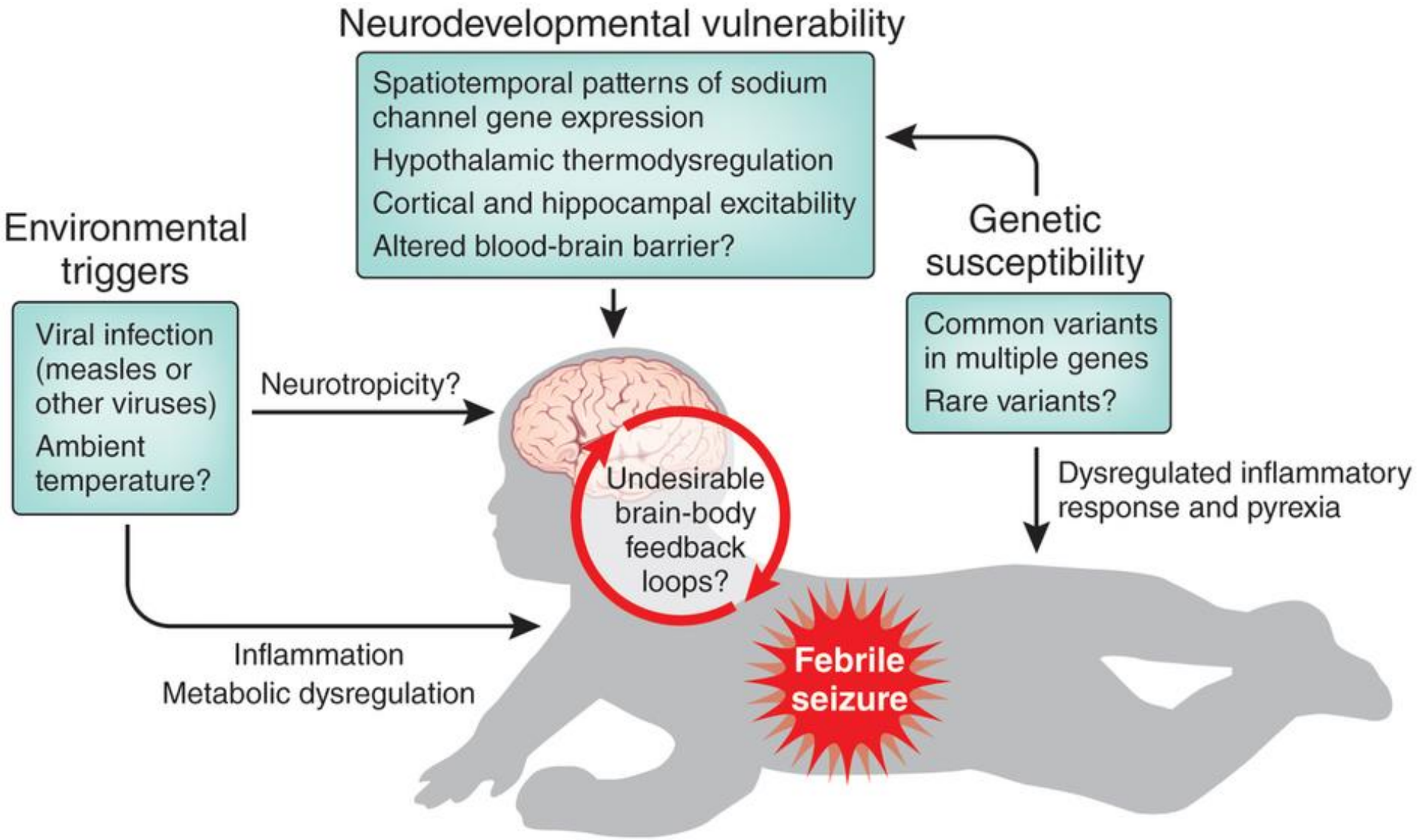




nature genetics
2014;46:1255-56

Feverish prospects for seizure genetics

Sanjay Sisodiya



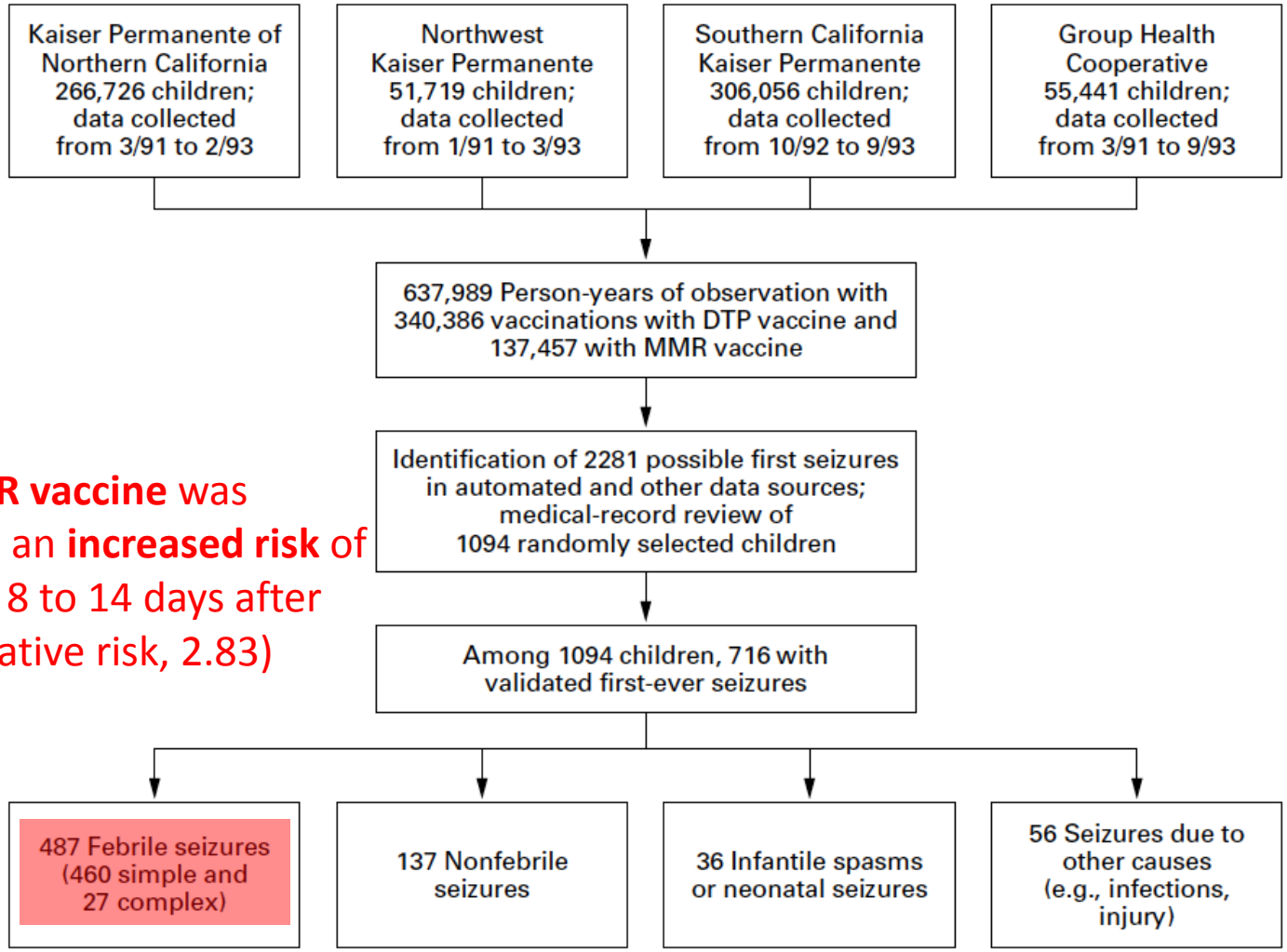
The NEW ENGLAND JOURNAL of MEDICINE

2001; 345:656-61.

The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine.

Barlow WE, Davis RL, Glasser JW, Rhodes PH, Thompson RS, Mullooly JP, Black SB, Shinefield HR, Ward JI, Marcy SM, DeStefano F, Chen RT, Immanuel V, Pearson JA, Vadheim CM, Rebolledo V, Christakis D, Benson PJ, Lewis N; Centers for Disease Control and Prevention Vaccine Safety Datalink Working Group.

Receipt of MMR vaccine was associated with an **increased risk** of ***febrile seizures*** 8 to 14 days after vaccination (relative risk, 2.83)



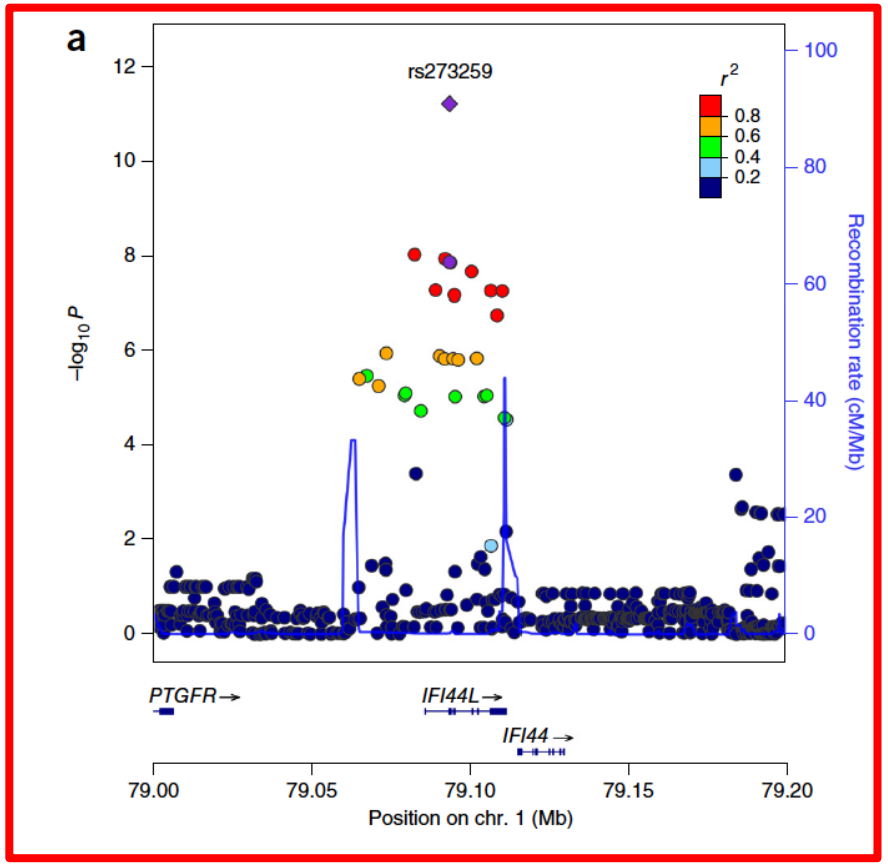
nature genetics
2014;46:1274-82

Common variants associated with general and MMR vaccine-related febrile seizures.

Feenstra B, Pasternak B, Geller F, Carstensen L, Wang T, Huang F, Eitson JL, Hollegaard MV, Svanström H, Vestergaard M, Hougaard DM, Schoggins JW, Jan LY, Melbye M, Hviid A.

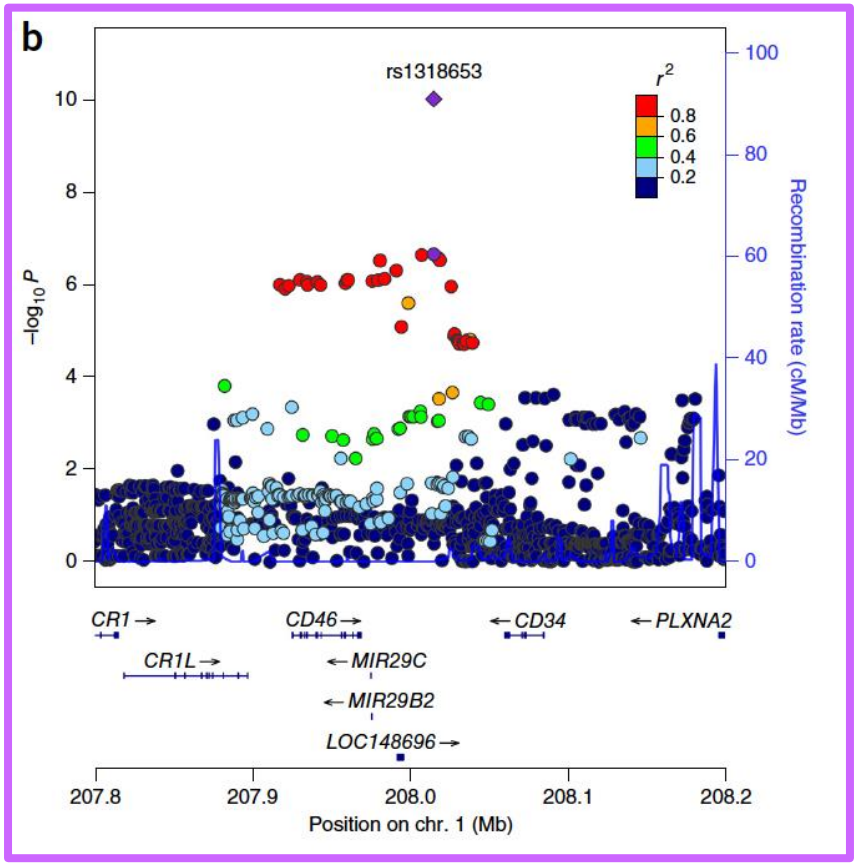
MMR-*related* febrile seizures

First locus on chromosome 1p31.1



The **gene *IFI44L*** *belongs to the group of interferon-stimulated genes*

Second locus on chromosome 1q32.2



The **gene *CD46*** *encodes a membrane protein of the complement system*

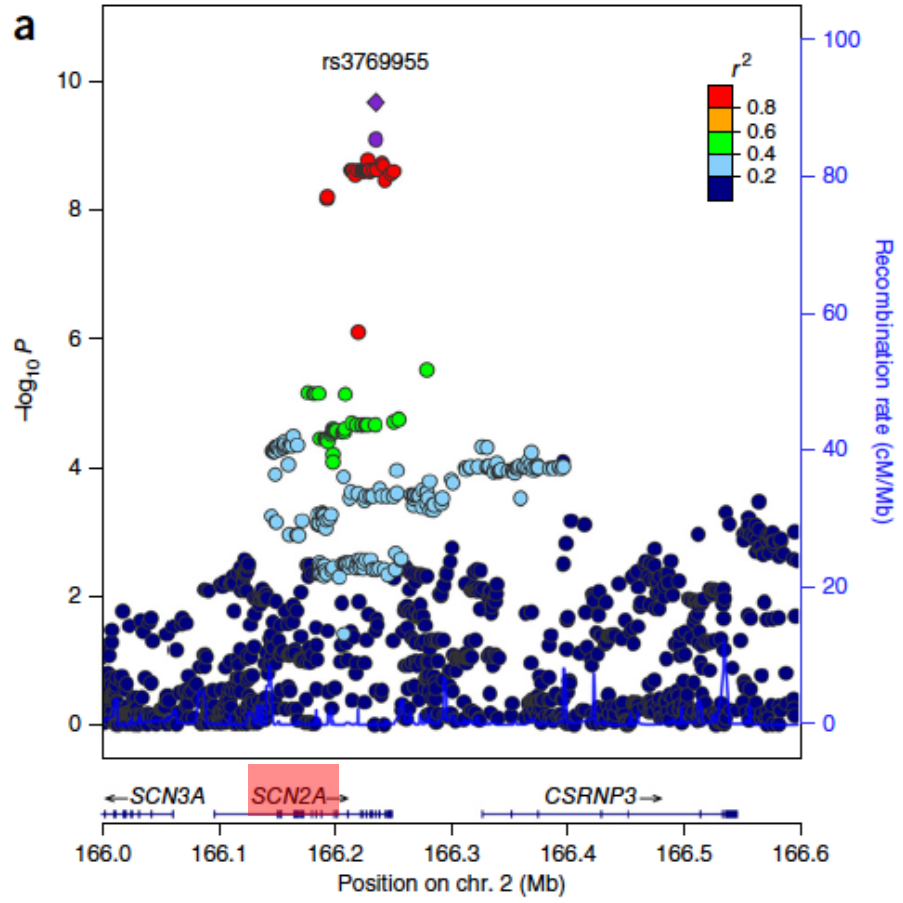
nature genetics
2014;46:1274-82

Common variants associated with general and MMR vaccine-related febrile seizures.

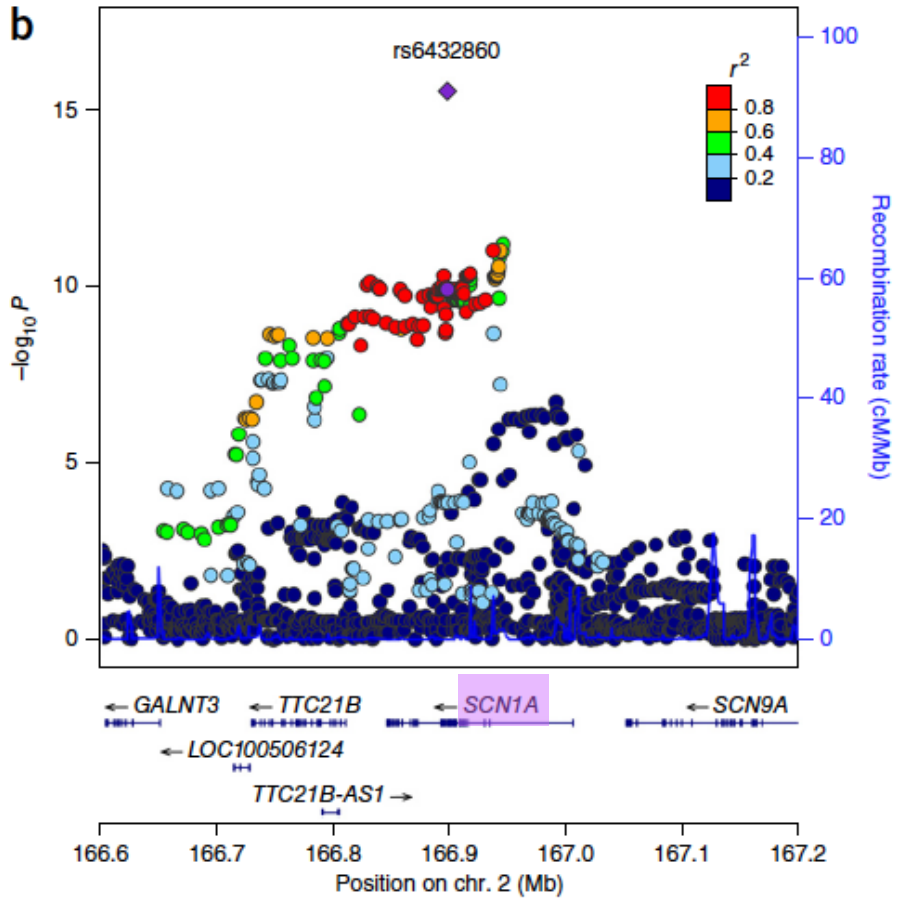
Feenstra B, Pasternak B, Geller F, Carstensen L, Wang T, Huang F, Eitson JL, Hollegaard MV, Svanström H, Vestergaard M, Hougaard DM, Schoggins JW, Jan LY, Melbye M, Hviid A.

MMR-*unrelated* febrile seizures

First locus on chromosome 2q24.3



Second locus on chromosome 2q24.3



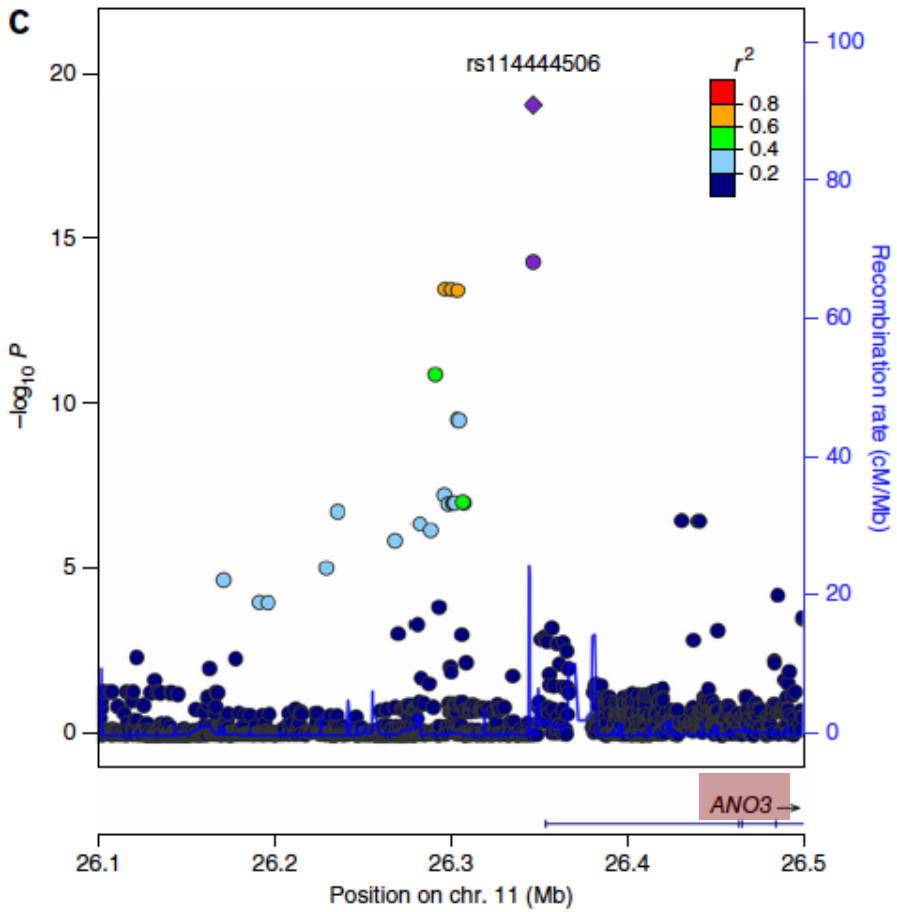
nature genetics
2014;46:1274-82

Common variants associated with general and MMR vaccine-related febrile seizures.

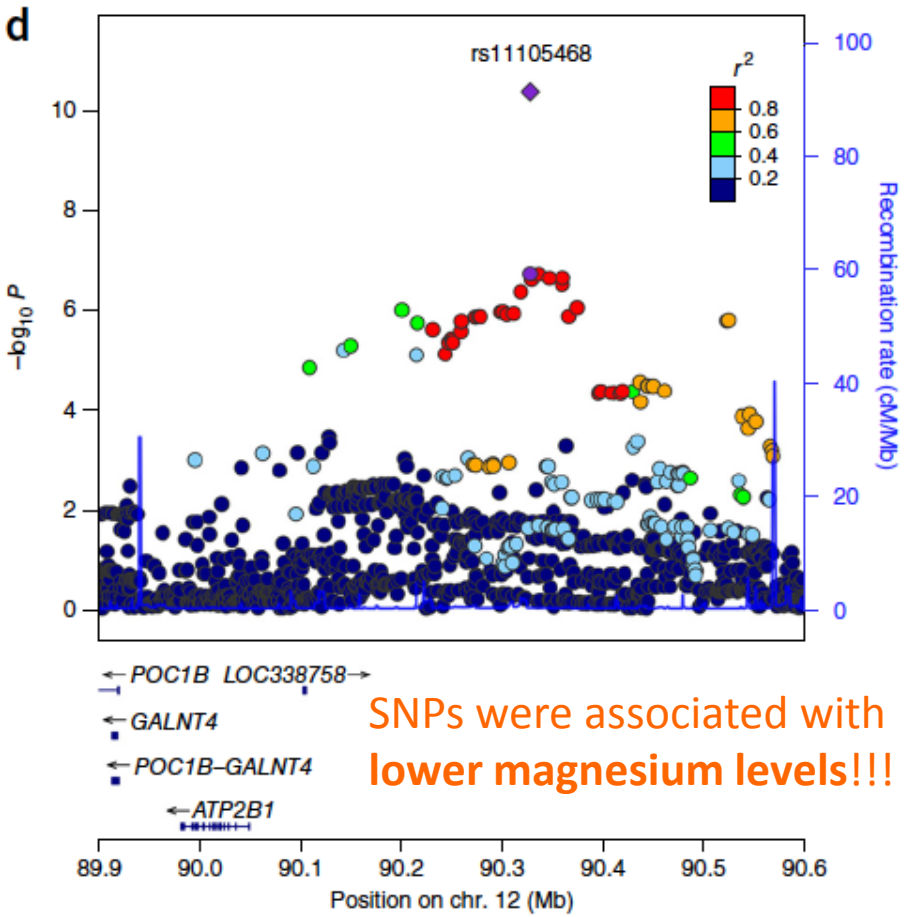
Feenstra B, Pasternak B, Geller F, Carstensen L, Wang T, Huang F, Eitson JL, Hollegaard MV, Svanström H, Vestergaard M, Hougaard DM, Schoggins JW, Jan LY, Melbye M, Hviid A.

MMR-*unrelated* febrile seizures

Third locus on chromosome 11p14.2



Fourth locus on chromosome 12q21.33



SNPs were associated with **lower magnesium levels**!!!

nature 2004; 428(6982):486
International weekly journal of science

Medical genetics: a marker for Stevens-Johnson syndrome

Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, Wu JY, Chen YT.

Frequency of *HLA* alleles in patients with Stevens-Johnson syndrome:

Table 1 **Frequency of *HLA* alleles in patients with Stevens–Johnson syndrome**

HLA allele	*CBZ–SJS*	*CBZ-tolerant*	*Normal*
*B*1502*	44 (100%)	3 (3%)*	8 (8.6%)†
*Cw*0801*	41 (93.2%)	17 (16.8%)	13 (14%)
*A*1101*	36 (81.8%)	51 (50.5%)	53 (57%)
*DRB1*1202*	33 (75%)	12 (11.9%)	18 (19.4%)
*B*1502, Cw*0801*	41 (93.2%)	3 (3%)	7 (7.5%)
*B*1502, A*1101*	36 (81.8%)	2 (2%)	6 (6.5%)
*B*1502, DRB1*1202*	33 (75%)	1(1%)	5 (5.4%)
*B*1502, Cw*0801, A*1101, DRB1*1202*	29(66%)	0 (0%)	3 (3.2%)

Frequencies (by number and percentage) of individual or combined loci of the *B*1502* ancestral haplotype are shown in patients with carbamazepine-induced Stevens–Johnson syndrome (CBZ–SJS; $n = 44$), and in carbamazepine-tolerant ($n = 101$) and normal subjects ($n = 93$). For methods, see supplementary information.

*Odds ratio (CBZ–SJS/CBZ-tolerant): 2,504 (95% CI, 126–49,522); corrected *P* value $P_c = 3.13 \times 10^{-27}$.

†Odds ratio (CBZ–SJS/normal): 895 (95% CI, 50–15,869); $P_c = 1.38 \times 10^{-21}$.

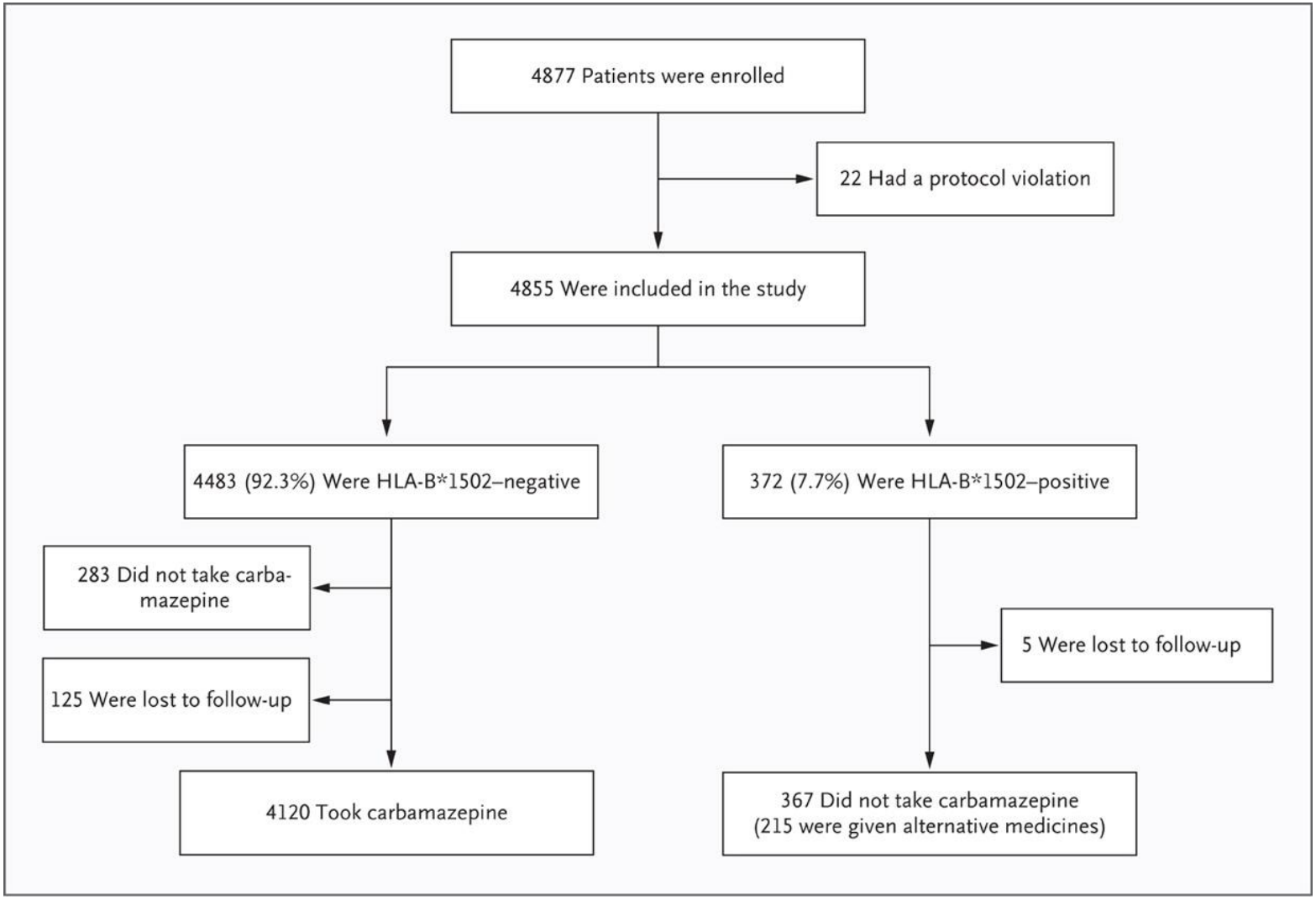
Strong association in Han Chinese between the human leukocyte **antigen HLA-B*1502**, and **Stevens-Johnson syndrome induced by carbamazepine**

The NEW ENGLAND JOURNAL of MEDICINE

2011;364:1126-33.

Carbamazepine-Induced Toxic Effects and HLA-B*1502 Screening in Taiwan

Chen P, Lin JJ, Lu CS, Ong CT, Hsieh PF, Yang CC, Tai CT, Wu SL, Lu CH, Hsu YC, Yu HY, Ro LS, Lu CT, Chu CC, Tsai JJ, Su YH, Lan SH, Sung SF, Lin SY, Chuang HP, Huang LC, Chen YJ, Tsai PJ, Liao HT, Lin YH, Chen CH, Chung WH, Hung SI, Wu JY, Chang CF, Chen L, Chen YT, Shen CY; Taiwan SJS Consortium.



The NEW ENGLAND JOURNAL of MEDICINE 2011;364:1126-33.

Table 2. Adverse Events during the 2-Month Follow-up.

Adverse Event	HLA-B*1502–Positive with Alternative Medication (N=215)	HLA-B*1502–Negative with Carbamazepine (N=4120)	Total
		number of events	
Mild cutaneous events			
Rash and itching	5*	206	211
Rash, itching, and blisters	1†	20	21
Rash, itching, and oral ulcers	0	14	14
Rash, itching, blisters, and oral ulcers	0	7	7
Itching, blisters, and oral ulcers	0	2	2
Blisters and oral ulcers	0	3	3
Severe cutaneous events			
Maculopapular eruption	0	3	3
Hypersensitivity syndrome	0	2	2
Urticaria	1‡	1	2
Stevens–Johnson syndrome or toxic epidermal necrolysis	0	0	0
Other adverse events§			
Fever	1	92	93
Sore throat	4	126	130
Fatigue	16	818	834
Dizziness	10	497	507
Insomnia	5	197	202
Gastrointestinal symptoms	4	185	189

* Among these 5 subjects, the alternative drugs were gabapentin, lamotrigine, naproxen, imipramine, and prednisolone.
† This subject had rash, itching, and blisters after taking gabapentin as an alternative treatment. These symptoms were mild and disappeared in 7 days.
‡ This subject had taken oxcarbazepine before study enrollment.
§ Subjects may have had more than one adverse event. Adverse events with a low frequency are not listed.

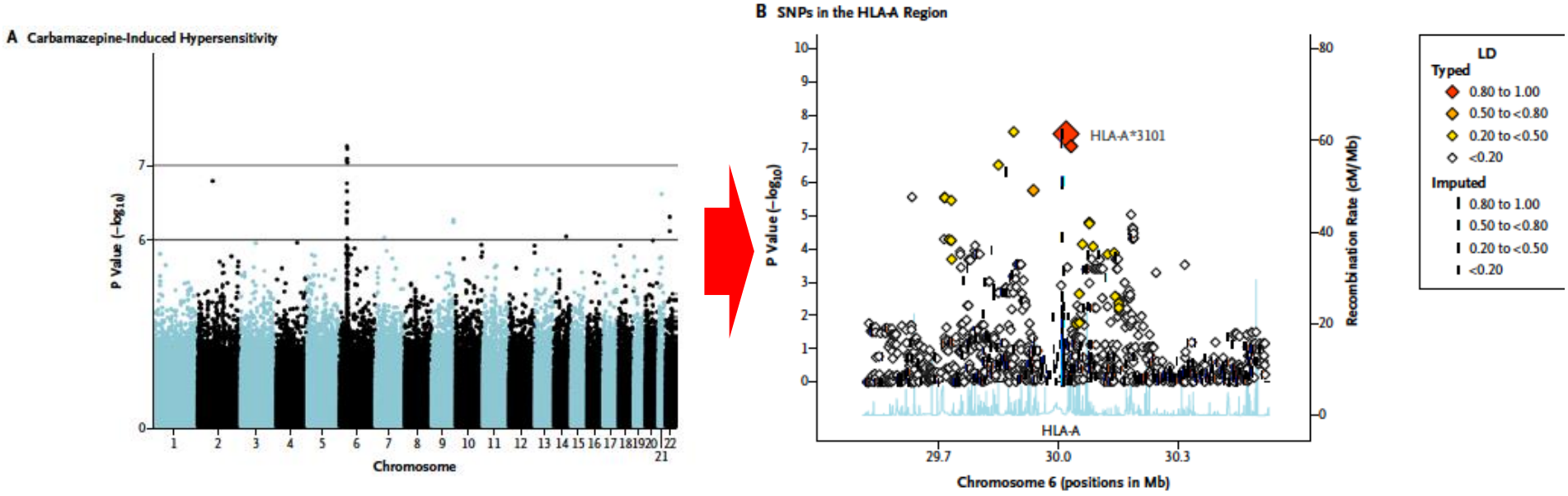
The NEW ENGLAND JOURNAL of MEDICINE

2011;364:1134-43.

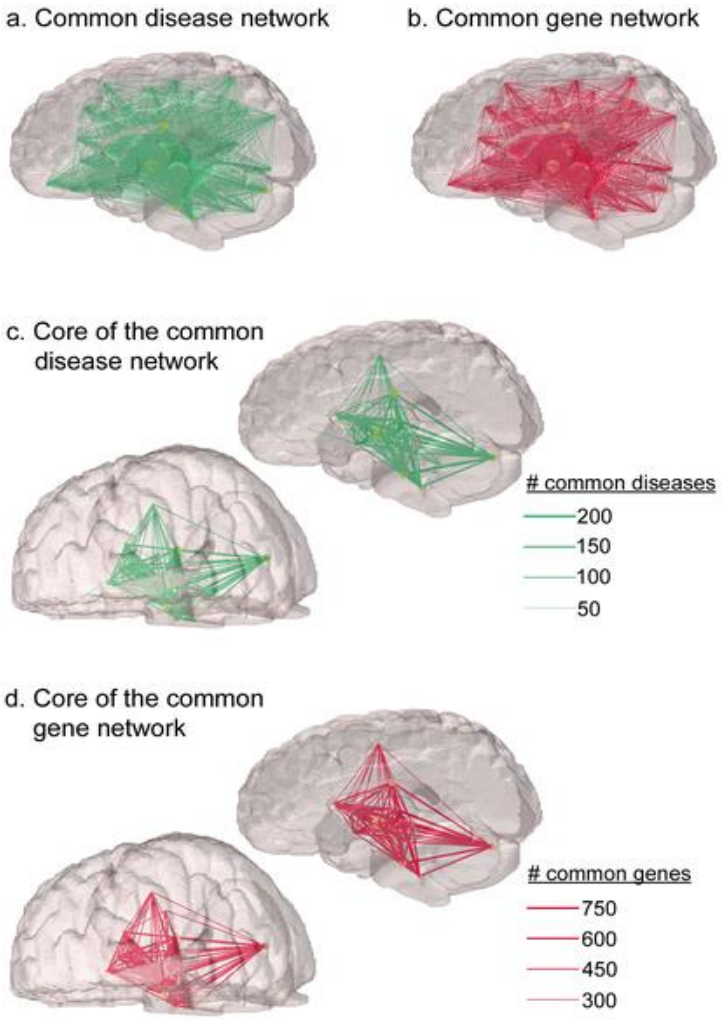
HLA-A*3101 and Carbamazepine-Induced Hypersensitivity Reactions in Europeans

McCormack M, Alfirevic A, Bourgeois S, Farrell JJ, Kasperavičiūtė D, Carrington M, Sills GJ, Marson T, Jia X, de Bakker PI, Chinthapalli K, Molokhia M, Johnson MR, O'Connor GD, Chaila E, Alhusaini S, Shianna KV, Radtke RA, Heinzen EL, Walley N, Pandolfo M, Pichler W, Park BK, Depondt C, Sisodiya SM, Goldstein DB, Deloukas P, Delanty N, Cavalleri GL, Pirmohamed M

Genomewide Association Study of Samples from **22 Case Subjects with Carbamazepine-Induced Hypersensitivity Syndrome** and 2691 Control Subjects.



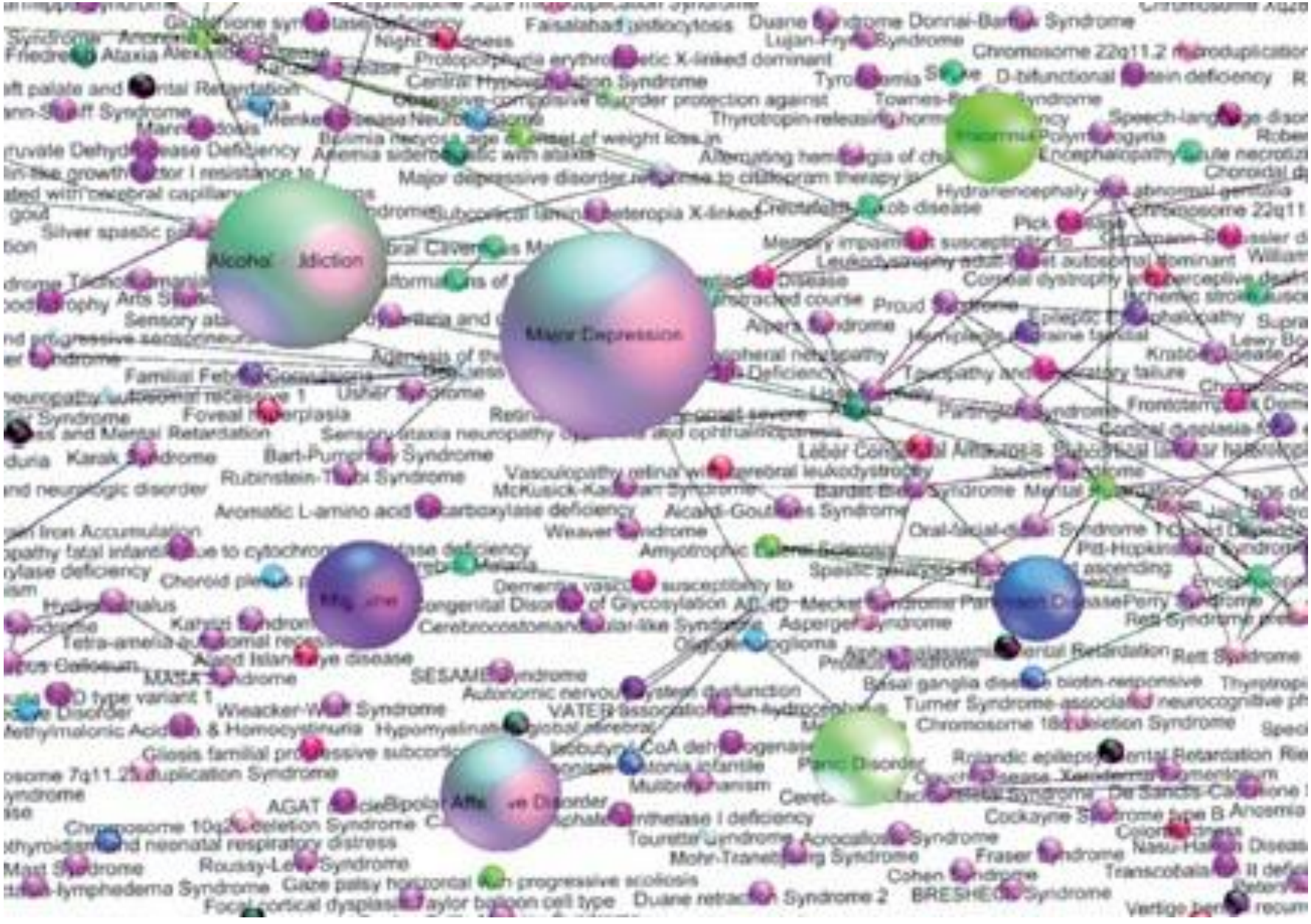
The common disease network and the common gene network.



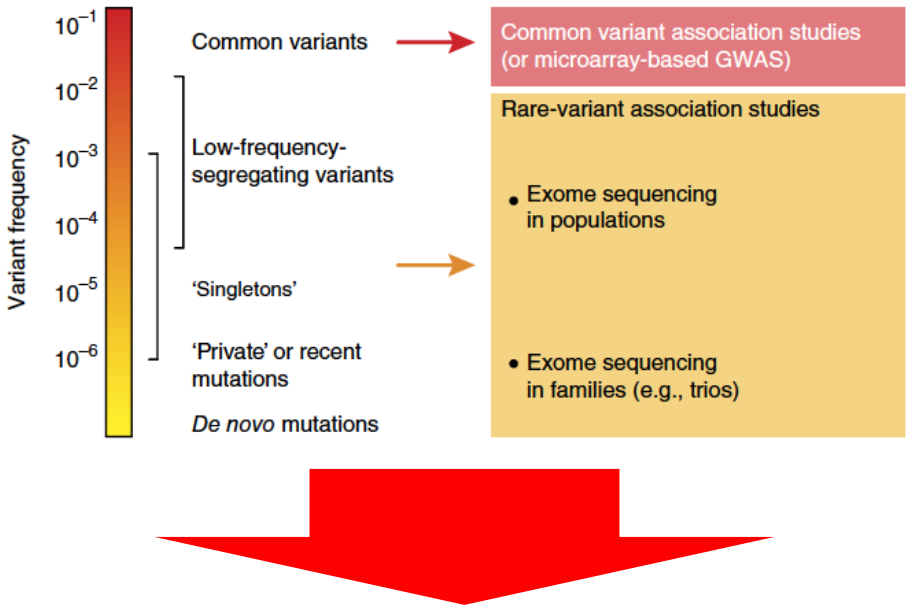
Hayasaka S, Hugenschmidt CE, Laurienti PJ (2011) A Network of Genes, Genetic Disorders, and Brain Areas. PLoS ONE 6(6): e20907. doi:10.1371/journal.pone.0020907

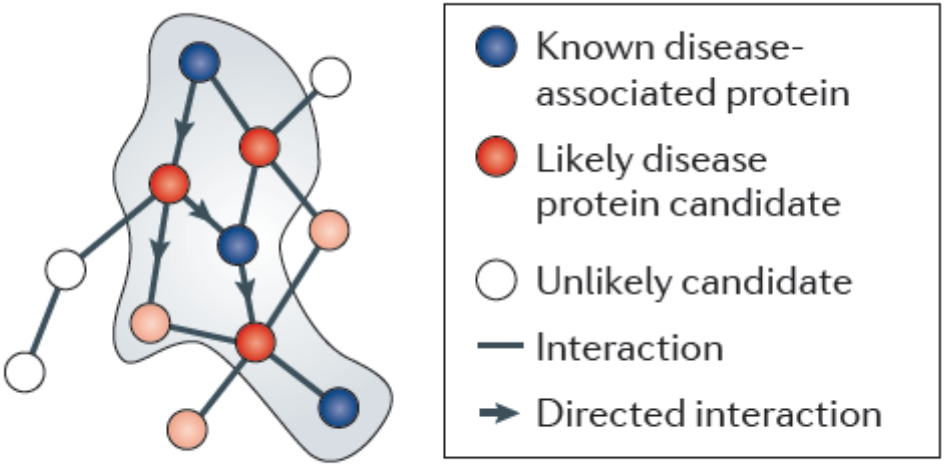
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0020907

Neuropsychiatry *diseasome*



Biological pathway



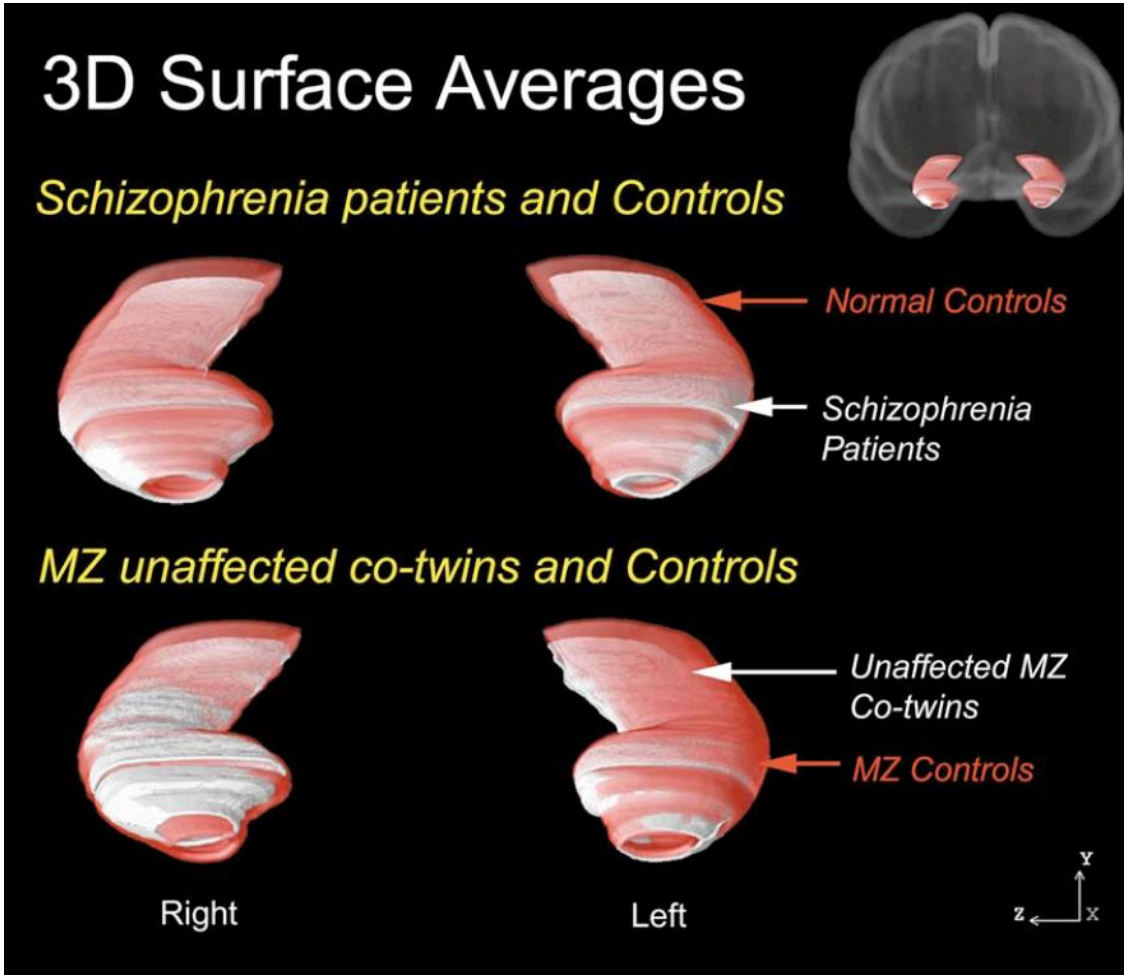


Predicted disease pathway

Neurobiology of Disease
2002;11(1):83-95

A twin study of genetic contributions to hippocampal morphology in schizophrenia.
Narr KL, van Erp TG, Cannon TD, Woods RP, Thompson PM, Jang S, Blanton R, Poutanen VP, Huttunen M, Lönnqvist J, Standerksjöld-Nordenstam CG, Kaprio J, Mazziotta JC, Toga AW.

Monozygotic, but not dizygotic, unaffected co-twins exhibited smaller left hippocampi



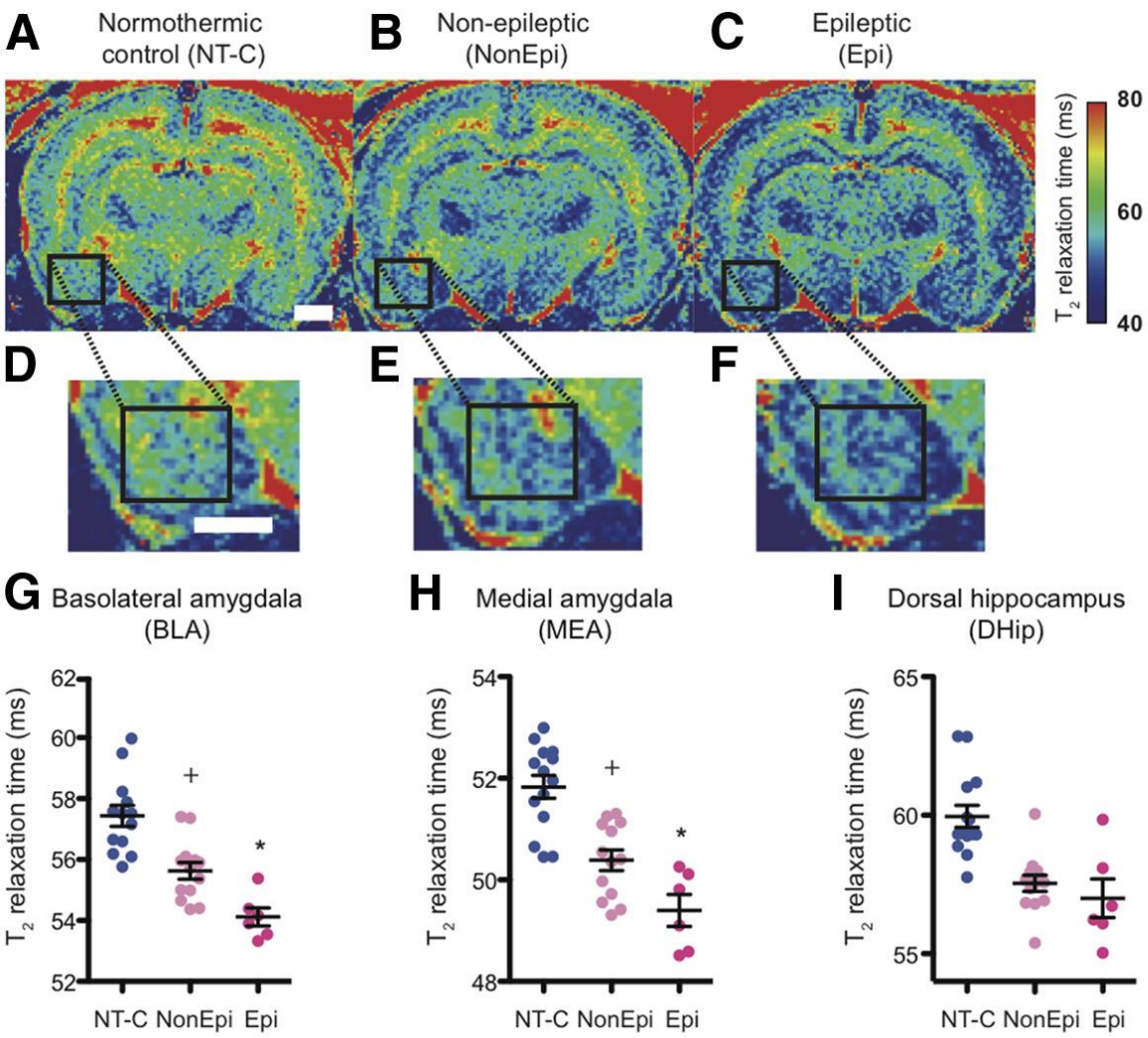
The Journal of Neuroscience

2014; 34:8672-84.

A novel, noninvasive, predictive epilepsy biomarker with clinical potential.

Choy M, Dubé CM, Patterson K, Barnes SR, Maras P, Blood AB, Hasso AN, Obenaus A, Baram TZ.

…reduced amygdala T2 relaxation times in high-magnetic-field MRI hours after FSE predicted experimental TLE.



ANNALS of Neurology
1996;40:227-235

Familial temporal lobe epilepsy: A common disorder identified in twins

Berkovic SF, McIntosh A, Howell A, Mitchell A, Sheffield LJ, Hopper JL.

We describe a new syndrome of familial temporal lobe epilepsy in **38 individuals from 13 unrelated white families**. The disorder was first identified in 5 concordant monozygotic twin pairs as part of a large-scale twin study of epilepsy. When idiopathic partial epilepsy syndromes were excluded, the 5 pairs accounted for 23% of monozygotic pairs with partial epilepsies, and 38% of monozygotic pairs with partial epilepsy and no known etiology. **Seizure onset for twin and nontwin subjects usually occurred during adolescence or early adult life.** **Seizure types were simple partial seizures with psychic or autonomic symptoms, infrequent complex partial seizures, and rare secondarily generalized seizures.** Electroencephalograms revealed sparse focal temporal interictal epileptiform discharges in 22% of subjects. **Magnetic resonance images appeared normal.** Nine affected family members (24%) had not been diagnosed prior to the study. Pedigree analysis suggested autosomal dominant inheritance with age-dependent penetrance. The estimated segregation ratio was 0.3, indicating an overall penetrance of 60% assuming autosomal dominant inheritance. **The mild and often subtle nature of the symptoms in some family members may account for lack of prior recognition of this common familial partial epilepsy.** This disorder has similarities to the El mouse, a genetic model of temporal lobe epilepsy with a major gene on mouse chromosome 9, which is homologous with a region on human chromosome 3.

ELSEVIER

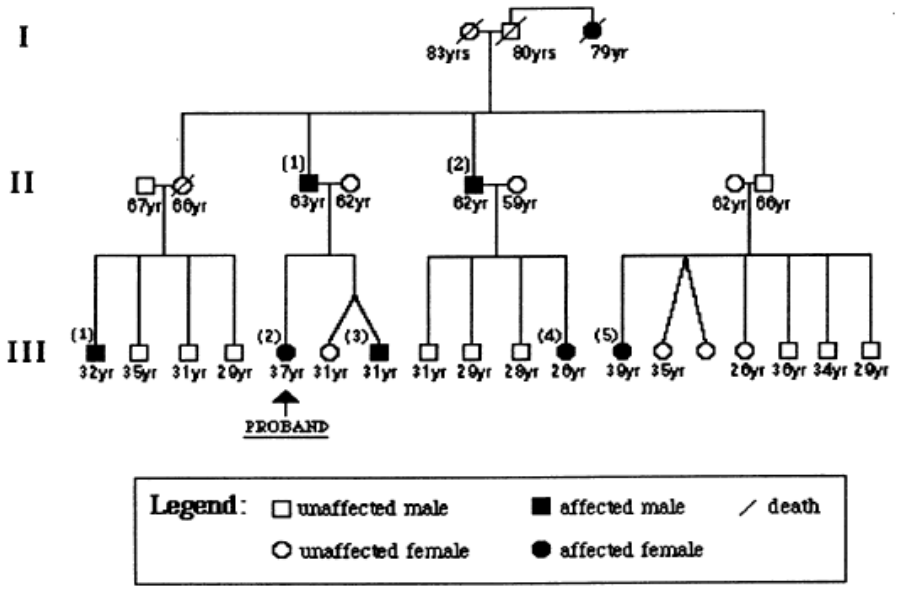
Epilepsy Research 38 (2000) 127–132

Epilepsy Research

www.elsevier.com/locate/epilepsyres

Familial temporal lobe epilepsy
Autosomal dominant inheritance in a large pedigree from Southern Italy☆

Antonio Gambardella [a,b,*], Demetrio Messina [a], Emilio Le Piane [a], R. Luciano Oliveri [a,b], Grazia Annesi [b], Mario Zappia [a], Eva Andermann [c], Aldo Quattrone [a,b], Umberto Aguglia [a]



Clinical, EEG and neuroradiological findings of the affected individuals

Patient *n.*, age, sex	Antecedent factors	Age at onset of epilepsy	Seizures type	Frequency	Interictal EEG	Imaging study	Therapy	Prognosis (follow-up)
II-1, 63 years, male	None	52 years	Rising epigastric sensation	Weekly	Normal	Normal (CT scan)	None	–
II-2 62 years, male	None	38 years	Fear, complex partial	Weekly 1/6–9 months	Left temporal delta waves	Normal (CT scan)	Carbamazepine (600 mg/daily)	sz. free (3 years)
III-1, 32 years, male	None	18 years	fear, confusion complex partial	Weekly, 3 in 9 years	Right temporal spiking	Normal (MR)	Phenytoin (300 mg/daily)	sz. free (3 years)
III-2, 37 years, female	Simple febrile convulsion (3 years)	17 years	Deja vu, complex partial, sec. Generalized	Weekly 1–3/ month, 2 in 19 years	Left temporal spiking	Normal (MR)	Carbamazepine (800 mg/daily)	sz. free (3 years)
III-3, 31 years, male	None	18 years	Fainting, deja vu, complex partial	2–3/6 months, 3 in 5 years	Normal	Normal (CT scan)	None[a]	sz. free (7 years)
III-4, 26 years, female	Head trauma with loss of consciousness (6 months)	19 years	Vegetative auras plus confusion, fear, complex partial, monthly, rare	Monthly, rare	Right temporal delta waves	Normal (MR)	Valproate (1.0 g/daily)	sz. free (3 years)
III-5, 39 years, female	None	30 years	Vegetative auras, complex partial	Weekly 1/3 years	Left temporal spiking	Normal (MR)	Carbamazepine (1.0 g/daily)	sz. free (4 years)

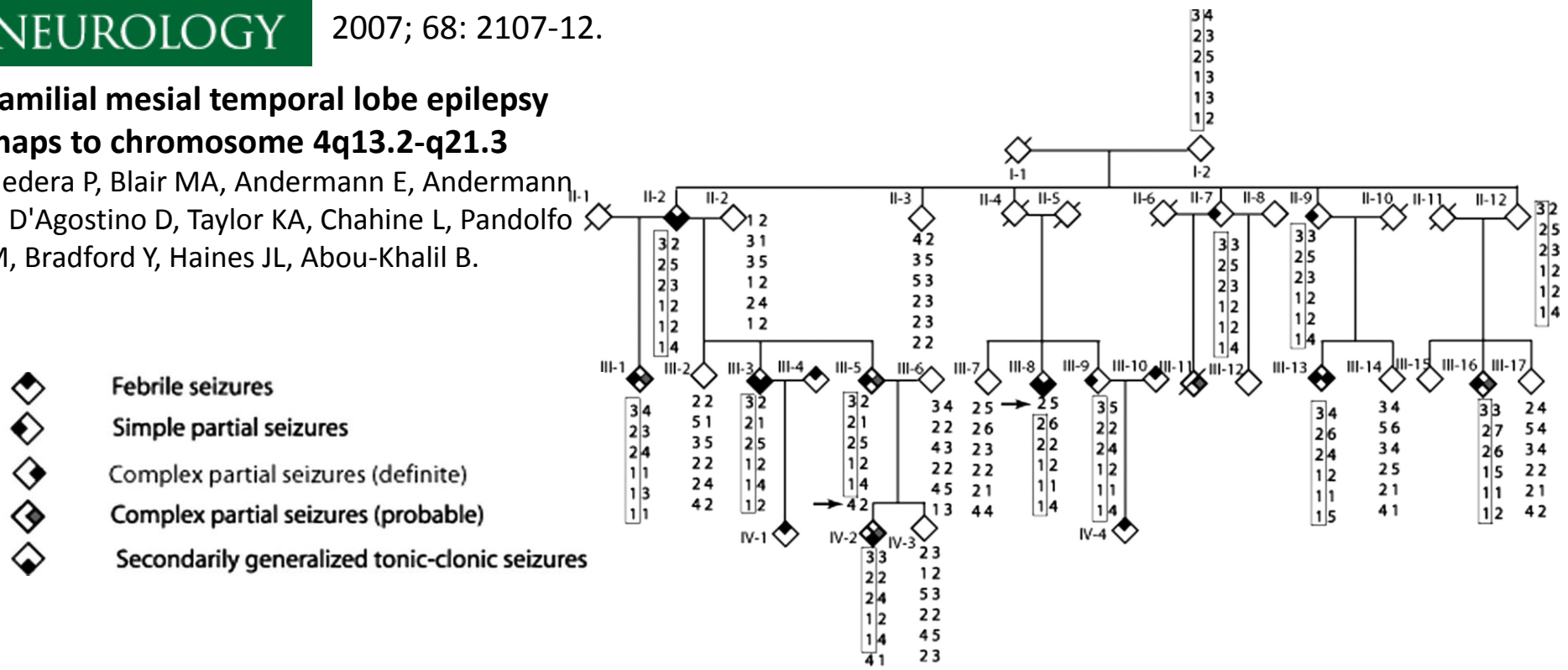
[a] From the age of 25 years he stopped valproate.

Five patients (II-2, III-2, III-3, III-4 and III-5) presented a history of migraine.

NEUROLOGY 2007; 68: 2107-12.

Familial mesial temporal lobe epilepsy maps to chromosome 4q13.2-q21.3

Hedera P, Blair MA, Andermann E, Andermann F, D'Agostino D, Taylor KA, Chahine L, Pandolfo M, Bradford Y, Haines JL, Abou-Khalil B.



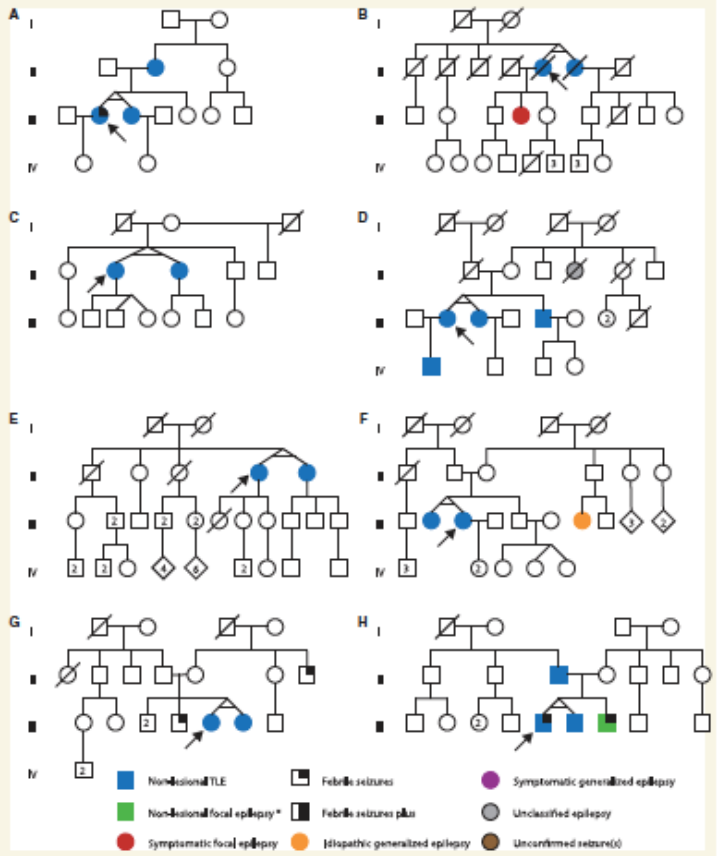
- **Inheritance was consistent with AD mode with reduced penetrance.**
- **Eleven individuals were classified as affected with FMTLE** and we also identified two living asymptomatic individuals who had affected offspring.
- **Seizure semiologies included predominantly SPS with deja vu feeling,** infrequent CPS, and rare secondarily generalized tonic-clonic seizures.
- **No structural abnormalities, including hippocampal sclerosis, were detected on MRI performed on three individuals.**
- **Genetic analysis detected a group of markers with lod score >3 on chromosome 4q13.2-q21.3 spanning a 7 cM region.**
- **No ion channel genes are predicted to be localized within this locus.**

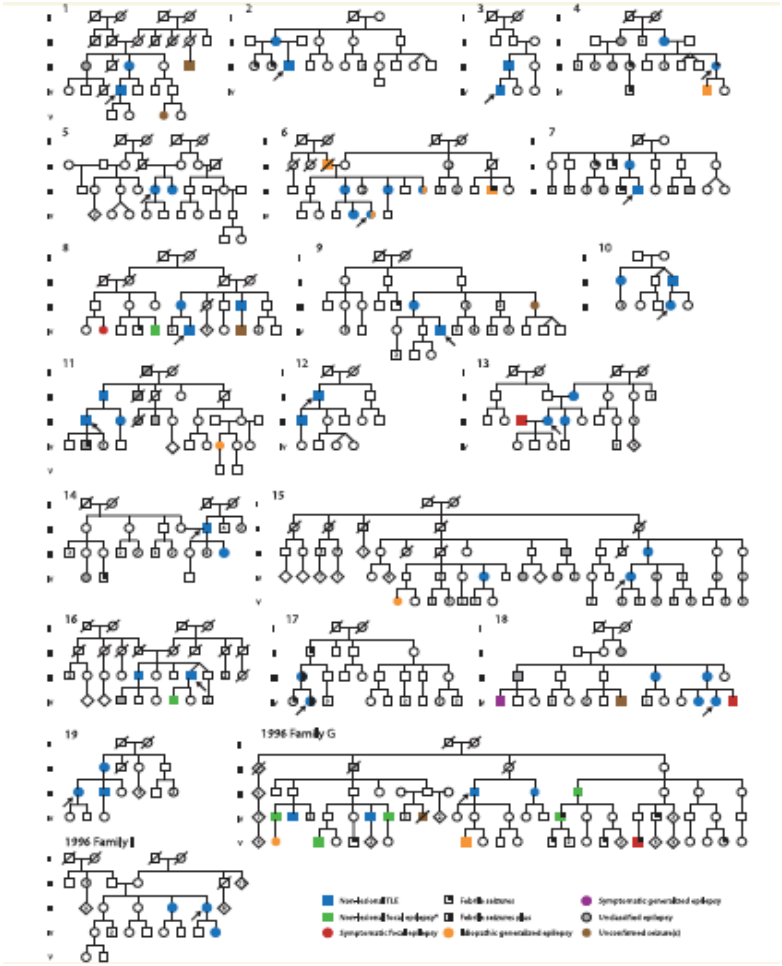
BRAIN
2010, 133: 3221-31

Familial mesial temporal lobe epilepsy: a benign epilepsy syndrome showing complex inheritance.

Crompton DE, Scheffer IE, Taylor I, Cook MJ, McKelvie PA, Vears DF, Lawrence KM, McMahon JM, Grinton BE, McIntosh AM, Berkovic SF.

…. These findings strongly suggest that **complex inheritance**, similar to that widely accepted in the idiopathic generalized epilepsies, is **the usual mode of inheritance in familial mesial temporal lobe epilepsy**.





nature REVIEWS NEUROLOGY
2011; 7(4):237-40.

OPINION

Benign mesial temporal lobe epilepsy

Angelo Labate, Antonio Gambardella, Eva Andermann, Umberto Aguglia, Fernando Cendes, Samuel F. Berkovic and Frederick Andermann

Box 1 | Clinical features of bMTLE

- Onset in late adolescence or adulthood
- Normal neurological examination
- Normal cognitive examination
- Unremarkable past medical history
- ≈30% have positive family history of febrile seizures or epilepsy
- ≈15% have personal antecedents of simple febrile seizures
- Viscerosensory auras are the predominant symptoms
- Easily controlled with a single antiepileptic drug
- Misdiagnosis of panic attacks or gastrointestinal disturbances is very common

Abbreviation: bMTLE, benign mesial temporal lobe epilepsy.

A benign form of mesial TLE (bMTLE) does exist and represents a common but often unrecognized clinical entity…

Box 2 | EEG, MRI and genetics of bMTLE

- ≥60% have normal interictal EEG
- Almost 40% have MRI evidence of hippocampal sclerosis
- Genetic predisposition is known to exist
- Remarkable intrafamilial and interfamilial phenotypic heterogeneity
- Autosomal dominant inheritance is rare

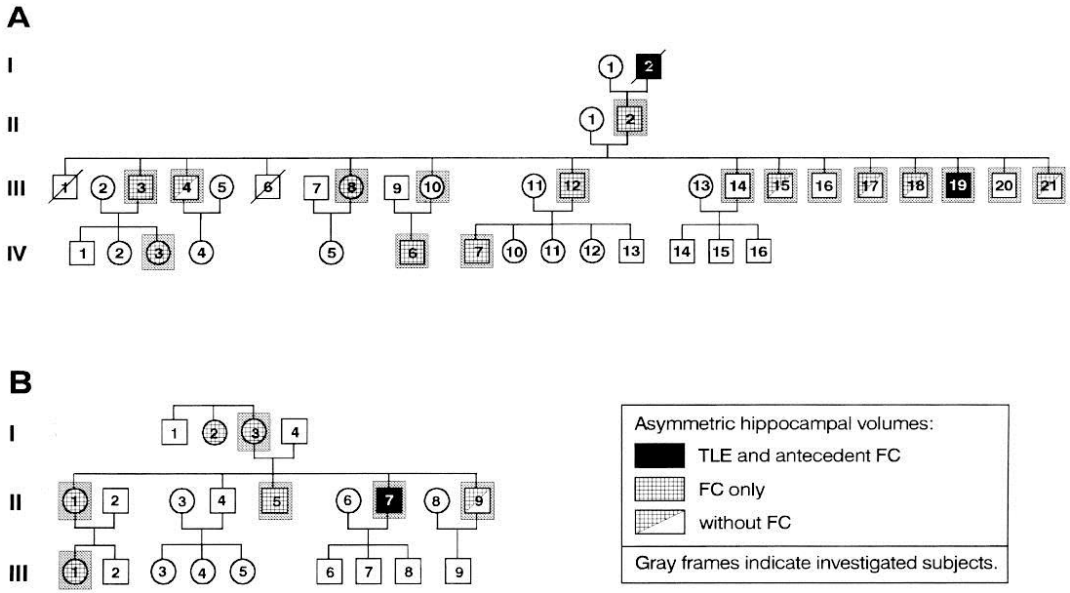
Abbreviation: bMTLE, benign mesial temporal lobe epilepsy.

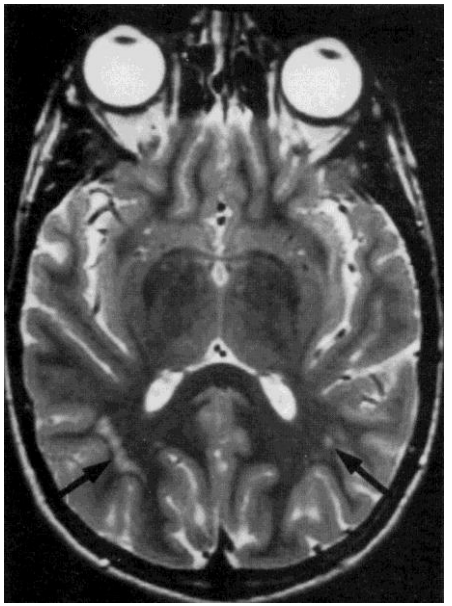
NEUROLOGY

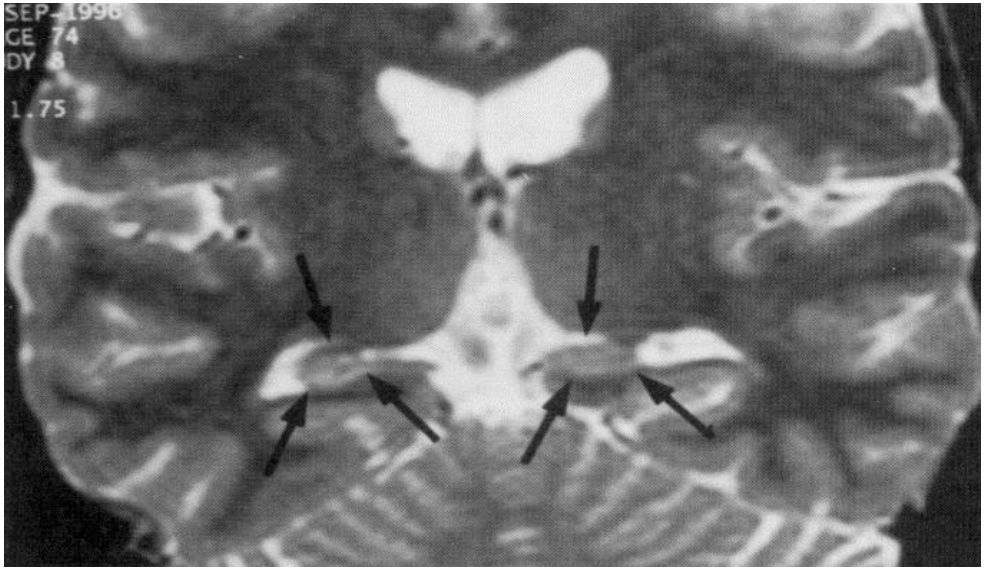
1998;50:909-17.

Hippocampal malformation as a cause of familial febrile convulsions and subsequent hippocampal sclerosis

Fernández G, Effenberger O, Vinz B, Steinlein O, Elger CE, Döhring W, Heinze H J.





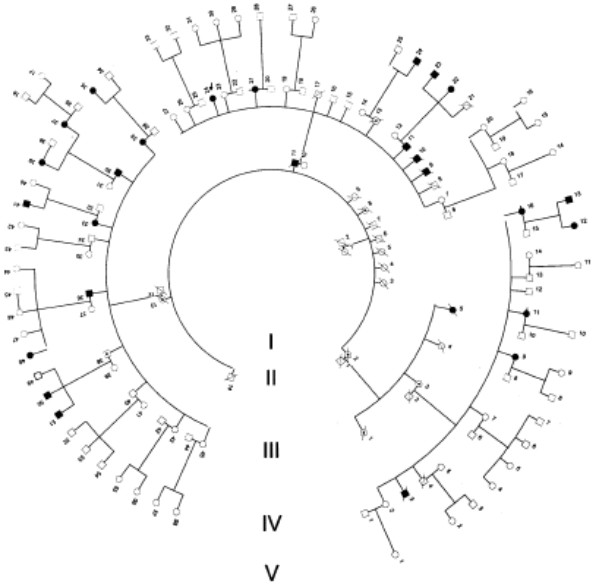


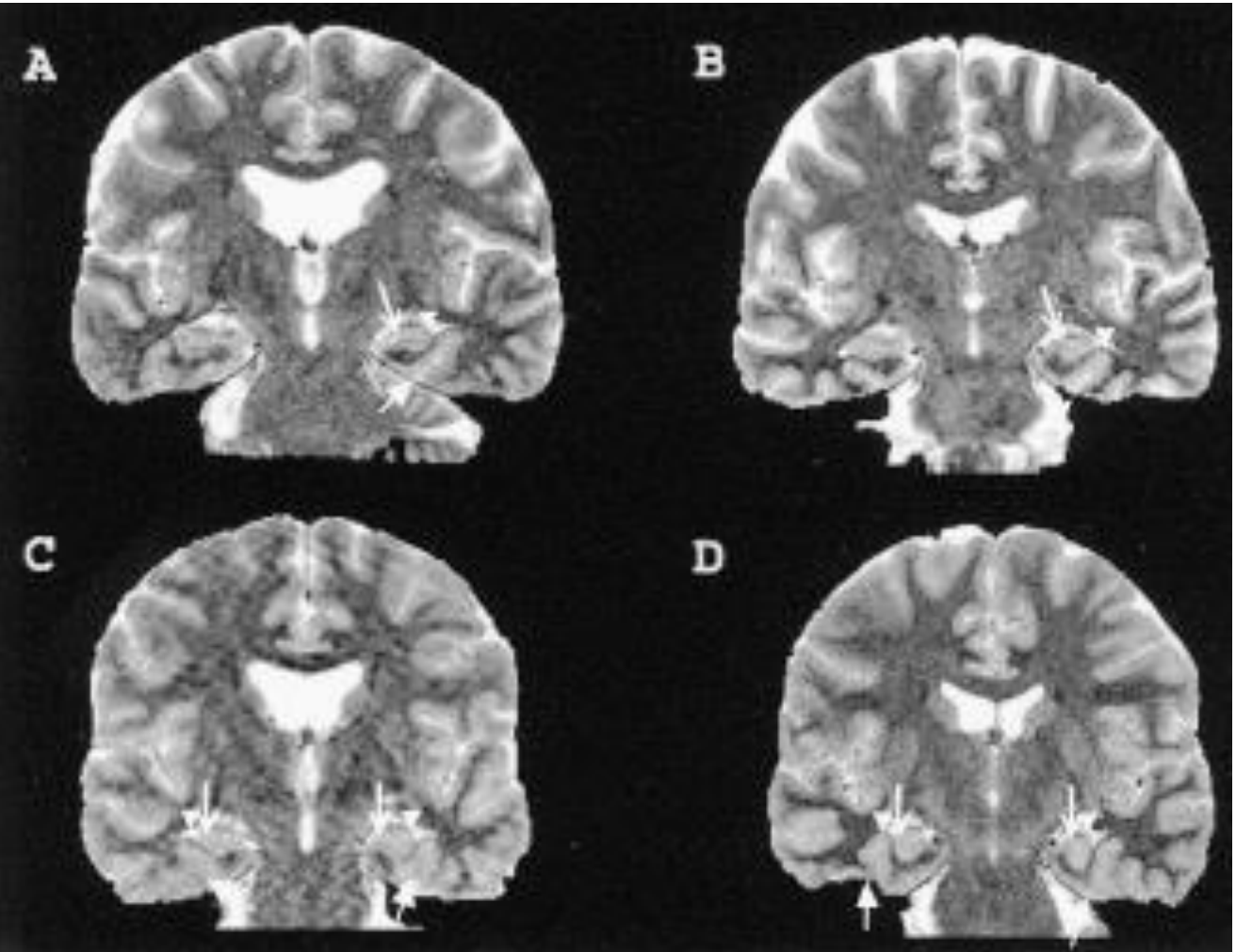
These findings suggest a subtle, pre-existing hippocampal malformation that may facilitate febrile convulsions and contribute to the development of subsequent HS.

NEUROLOGY 2002; 58:1429-33.

Familial temporal lobe epilepsy with febrile seizures

Depondt C, Van Paesschen W, Matthijs G, Legius E, Martens K, Demaerel P, Wilms G.





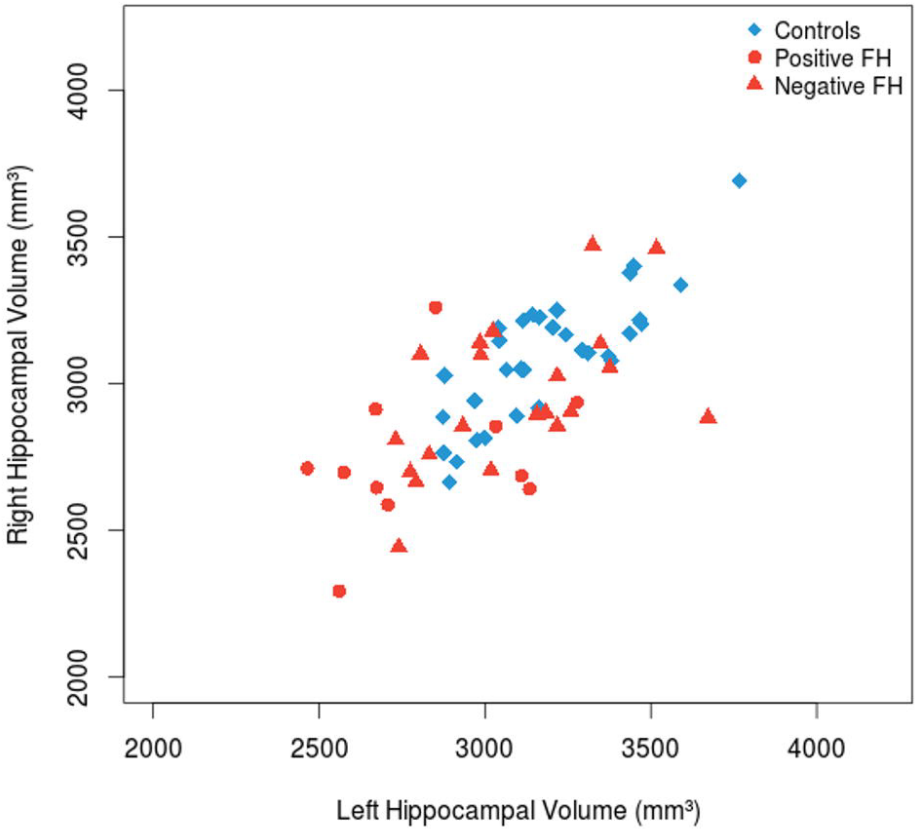
(**A**) and (**B**) show unilateral **left hippocampal malrotation (HIMAL)** and **(C)** and **(D) bilateral HIMAL.** Note the abnormally steep angles of the collateral sulci (small closed arrows), the abnormally rounded shapes of the hippocampi (large open arrows), and the abnormal configurations of the temporal horns (arrowheads).

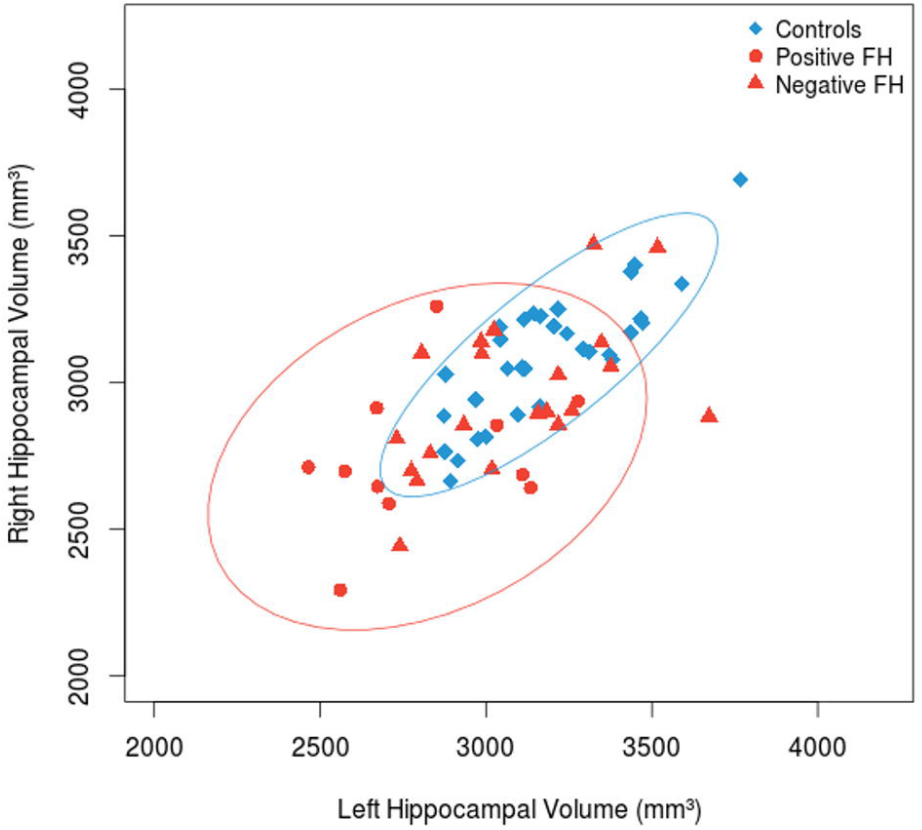
NEUROLOGY
2013; 81(2):144-9

Etiology of hippocampal sclerosis: evidence for a predisposing familial morphologic anomaly.

Tsai MH, Pardoe HR, Perchyonok Y, Fitt GJ, Scheffer IE, Jackson GD, Berkovic SF.

N° **32 asymptomatic relatives** from 15 families in which probands had TLE with HS and 32 age- and sex-matched controls





NEUROLOGY

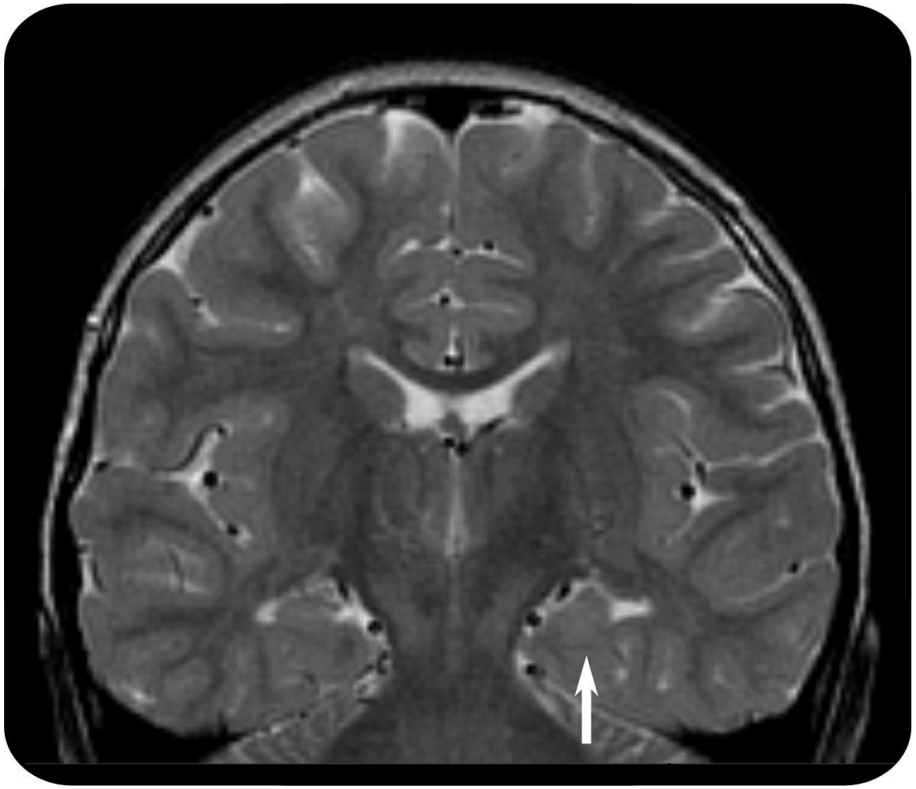
2012; 79(9):871-877

MRI abnormalities following febrile status epilepticus in children: the FEBSTAT study.

Shinnar S, Bello JA, Chan S, Hesdorffer DC, Lewis DV, Macfall J, Pellock JM, Nordli DR, Frank LM, Moshe SL, Gomes W, Shinnar RC, Sun S; FEBSTAT Study Team

Developmental abnormalities of the hippocampus were more common in the FSE group (n 20, 10.5%) than in controls (n 2, 2.1%) (p 0.0097) with ***hippocampal malrotation being the most common*** (15 cases and 2 controls).

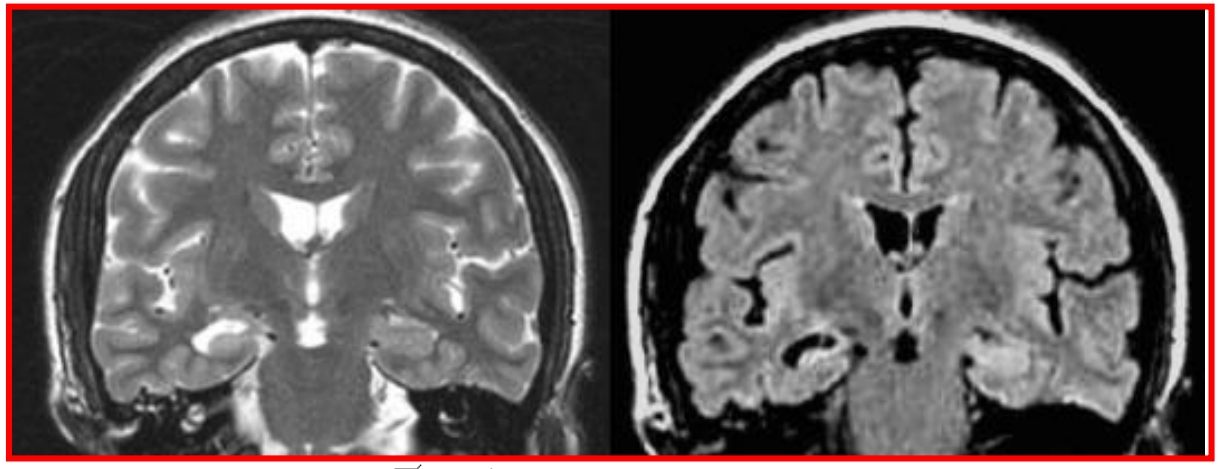
Hippocampal malrotation in a 40-month-old child with febrile status epilepticus

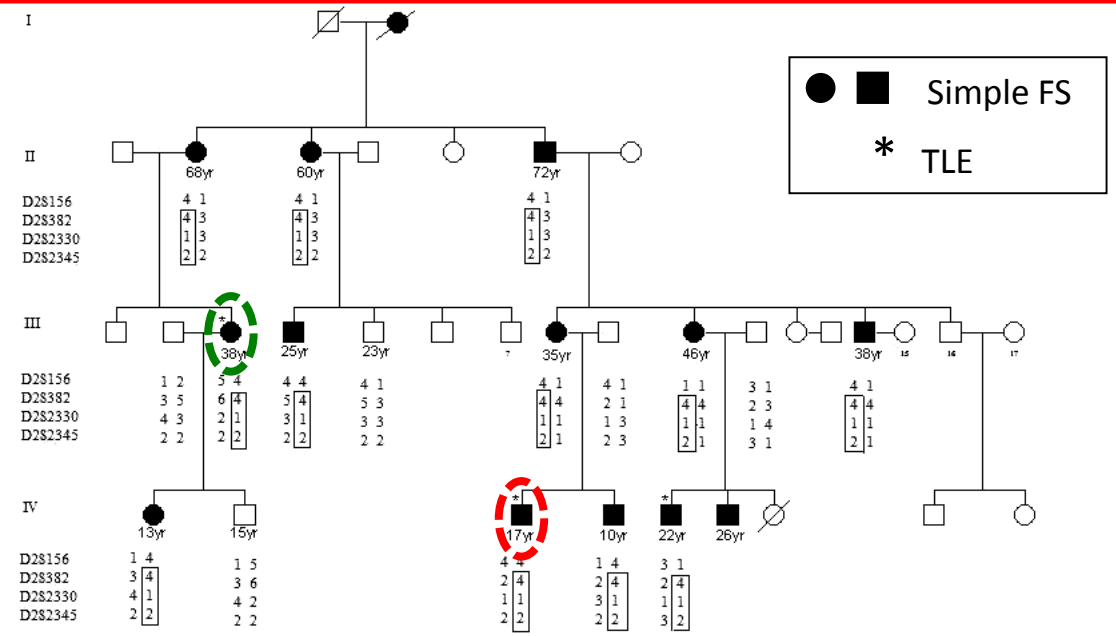


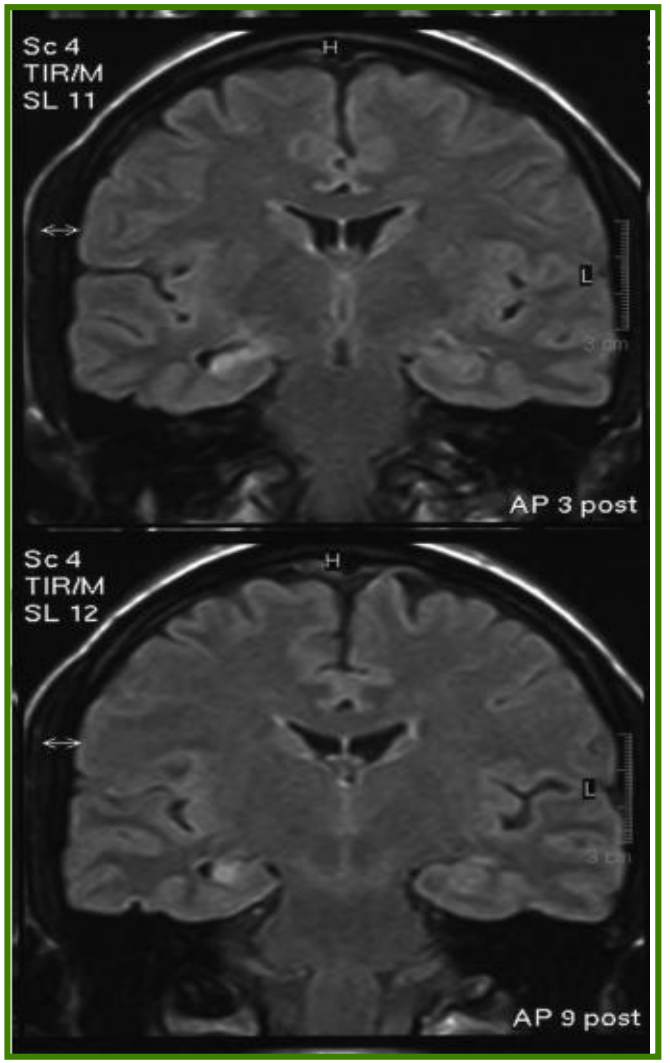
Epilepsia
2007;48:1691-6

Electroclinical Features of a Family with Simple Febrile Seizures and Temporal Lobe Epilepsy Associated with SCN1A Loss-of-Function Mutation

Colosimo E, Gambardella A, Mantegazza M, Labate A, Rusconi R, Schiavon E, Annesi F, Cassulini RR, Carrideo S, Chifari R, Canevini MP, Canger R, Franceschetti S, Annesi G, Wanke E, Quattrone A.





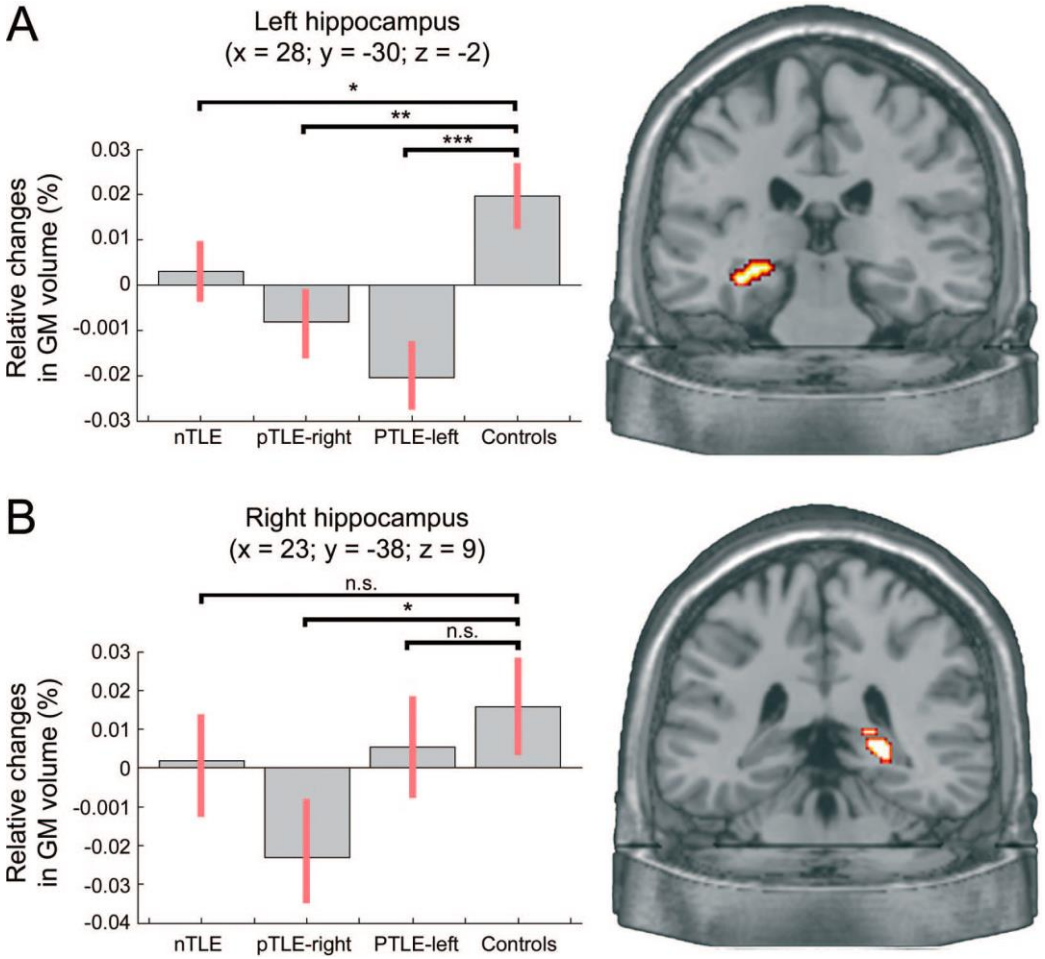


NEUROLOGY
2008;71:1094–1101

Hippocampal and thalamic atrophy in mild temporal lobe epilepsy A VBM study

Labate A, Cerasa A, Gambardella A*, Aguglia U, Quattrone A.

Volume of (A) left (peak voxel x, y, z28, 30, 2) and (B) right hippocampus (peak voxel x, y, z23, 38, 9)

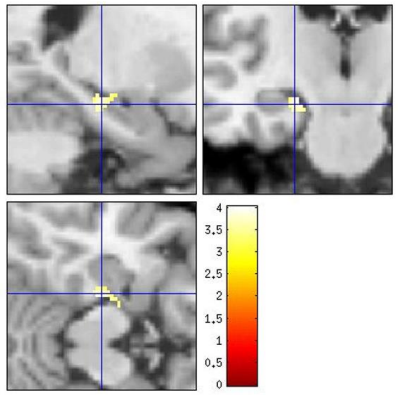


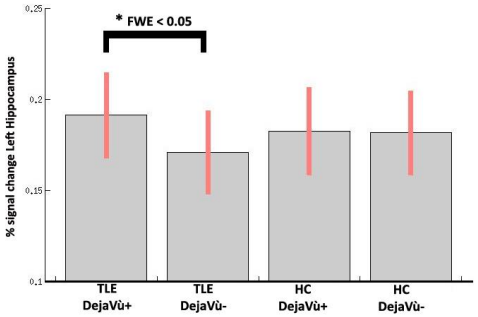
Cortex
A journal devoted to the study of the nervous system and behavior
2015;64:1-7

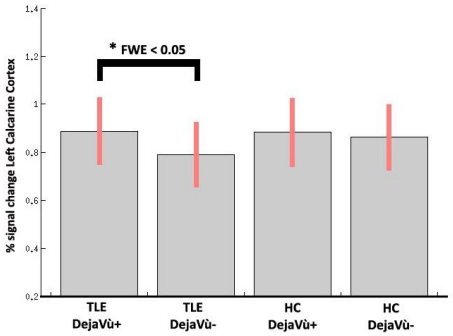
Neuro-anatomical differences among epileptic and non-epileptic déjà-vu

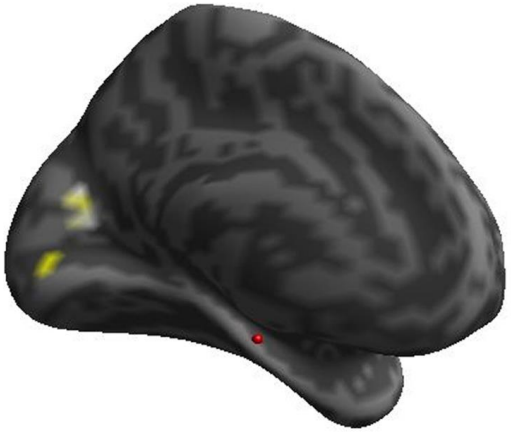
Labate A, Cerasa A, Mumoli L, Ferlazzo E, Aguglia U, Quattrone A, Gambardella A.

TLE patients with DV display **an abnormal increase of the gray matter** in the **left hippocampus** and calcarine cortex volume in comparison with those without DV.









ANNALS of Neurology

1982; 12:129-144

The Role of the Limbic System in Phenomena of Temporal Lobe Epilepsy

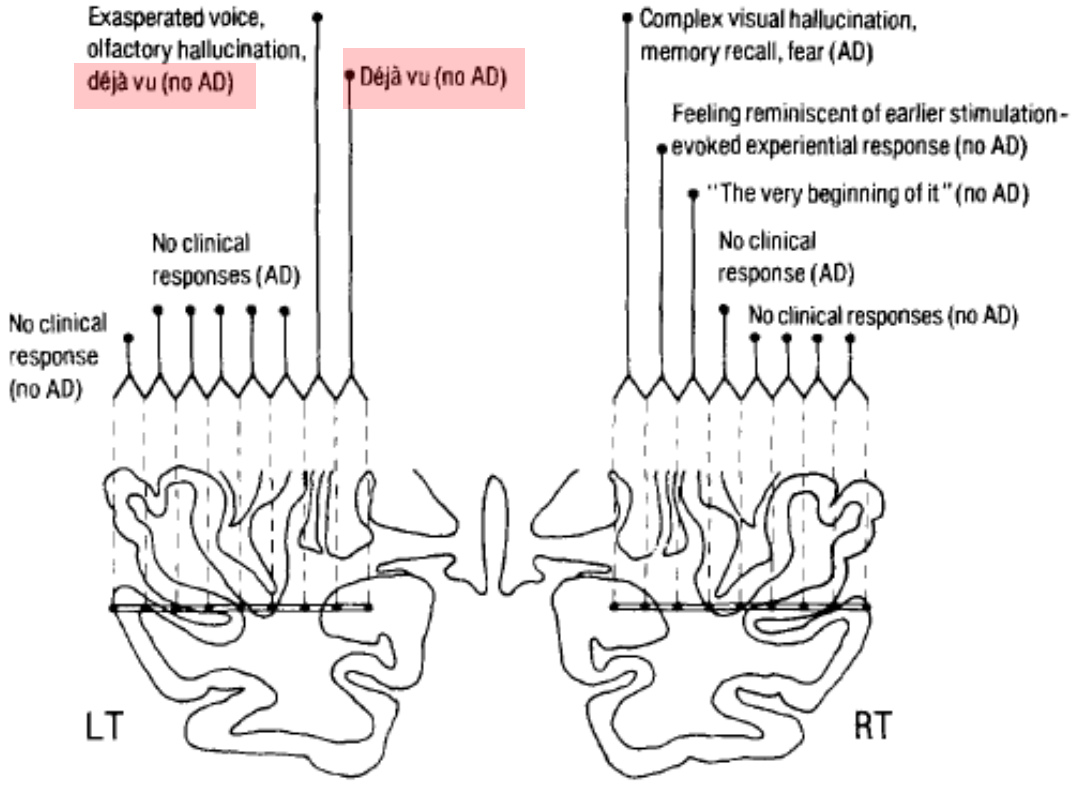
Pierre Gloor, Andre Olivier, Luis F. Quesney, Frederick Andermann, Sandra Horowitz

Experiential phenomena occurring in spontaneous seizures or evoked by brain stimulation were reported by **18 of 29 patients** who were investigated with chronic, stereotaxically implanted intracerebral electrodes.

Table 1. Experiential Illusions and Hallucinations Observed with Stereotaxic Exploration of the Temporal Lobes

Experience	No. of Observations	No. of Patients
Visual illusions	9	3
Elementary visual hallucinations (phosphenes)	15[a]	3
Complex visual hallucinations	18	5
Auditory illusions	0	0
Elementary auditory hallucinations	0	0
Complex auditory hallucinations	3	2
Olfactory hallucinations	2	1
Familiarity (déjà vu)	23	4
Unfamiliarity (jamais vu)	0	0
Memory recall	19	5
Forced thinking	10	2
Fear	>49	7
Anger	1[b]	1
Irritation	>3	1
Emotional distress (depression, guilt, etc)	6[c]	3
Far-away feeling	>3	1
Feeling of someone being nearby	1	1
Pleasant emotion	0	0
Sexual emotion	0	0
Thirst	10[d]	2
Hunger	0	0
Feeling of bodily distortion	2	1
Strange, indescribable feeling (mental)	2	2
Floating sensation (excitement? startle?)	7	1

Topographical distribution of responses obtained with electrical stimulations upplied to adjacent pairs of contacts



BRAIN A JOURNAL OF NEUROLOGY

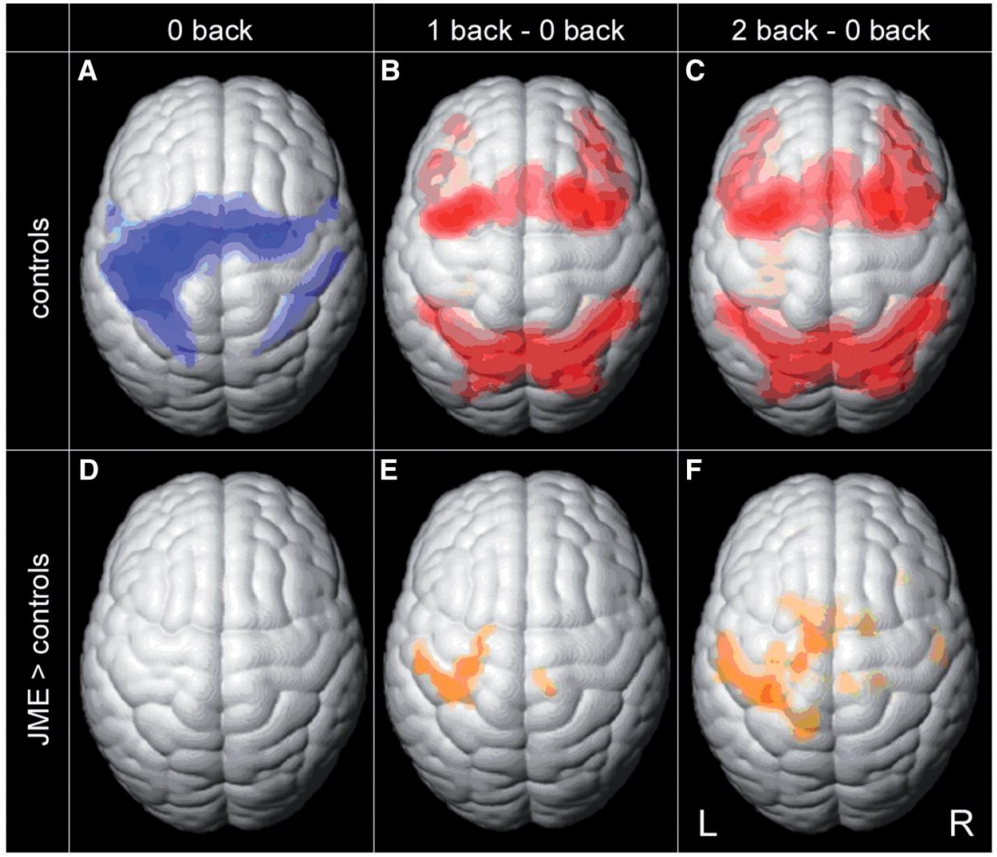
2011;135:3635-44

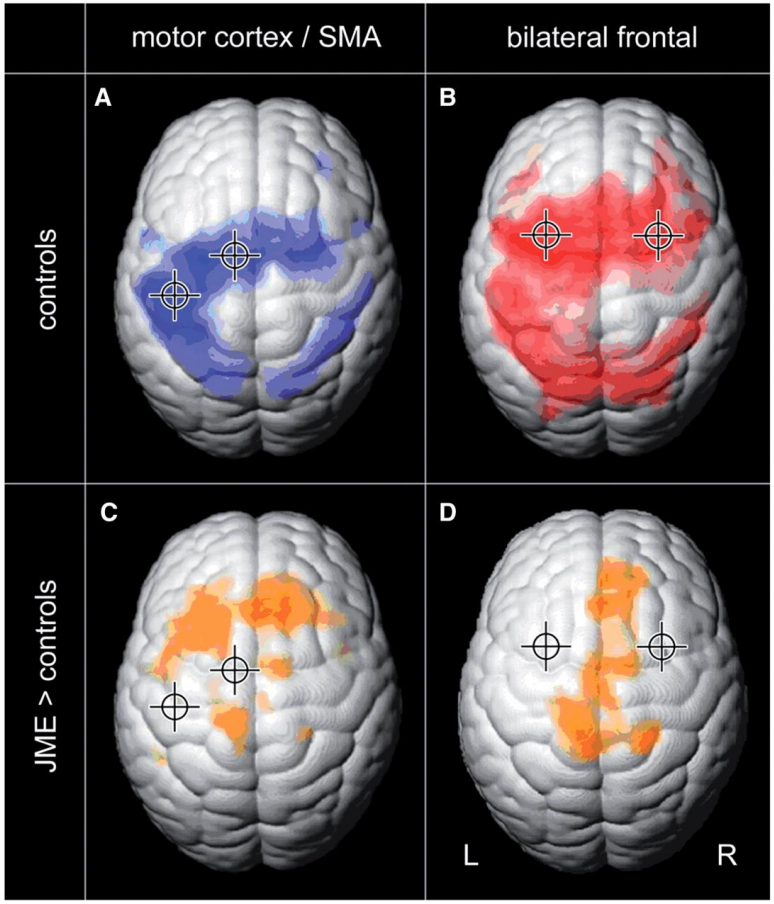
Motor system hyperconnectivity in juvenile myoclonic epilepsy: a cognitive functional magnetic resonance imaging study.

Vollmar C, O'Muircheartaigh J, Symms MR, Barker GJ, Thompson P, Kumari V, Duncan JS, Janz D, Richardson MP, Koepp MJ.

Functional connectivity is increased in JME.

Functional MRI activation from working memory task in controls and group differences.





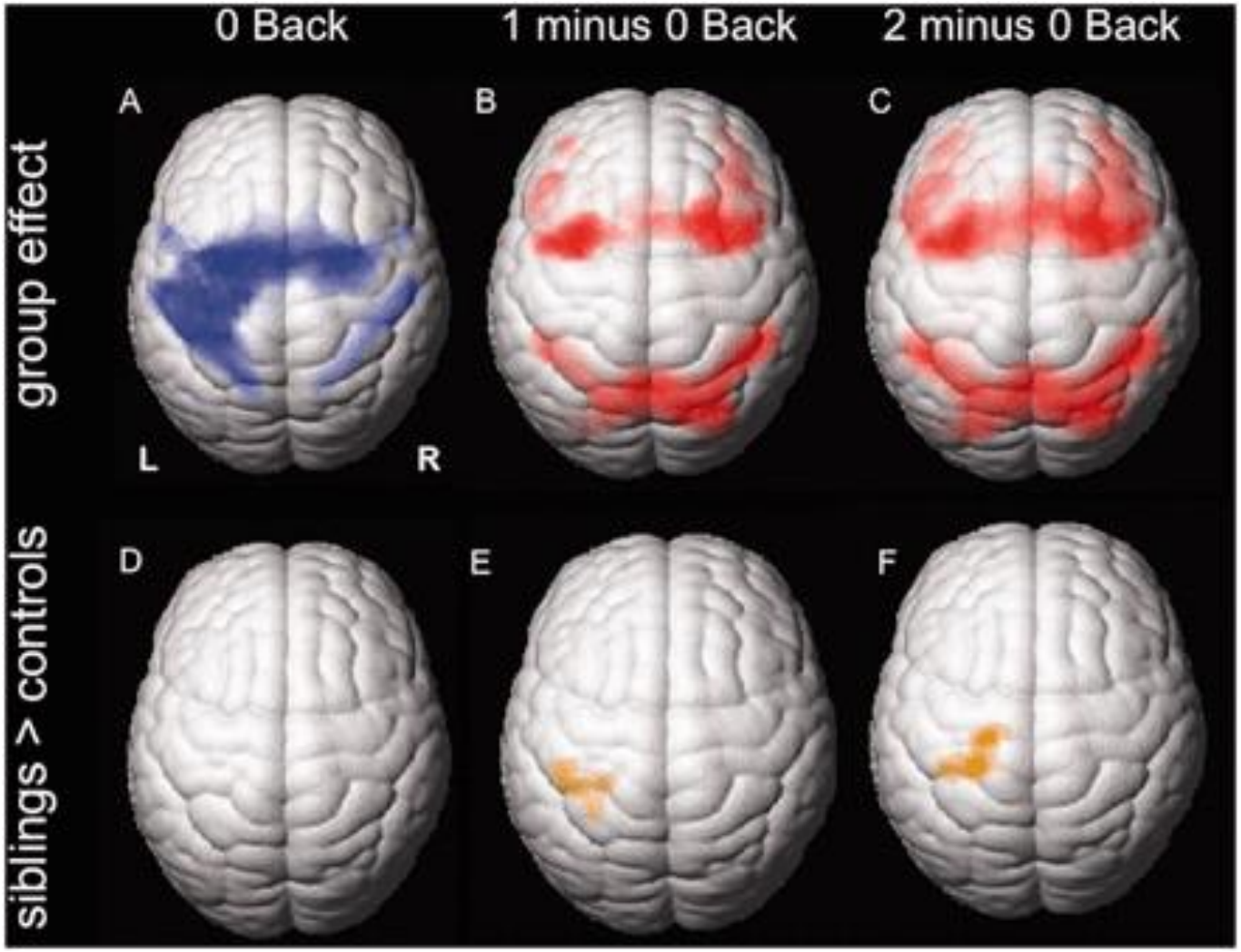
BRAIN A JOURNAL OF NEUROLOGY

2014;137:2469-79

Motor co-activation in siblings of patients with juvenile myoclonic epilepsy: an imaging endophenotype?

Wandschneider B, Centeno M, Vollmar C, Symms M, Thompson PJ, Duncan JS, Koepp MJ.

Functional MRI activation from working memory task in controls and group differences.

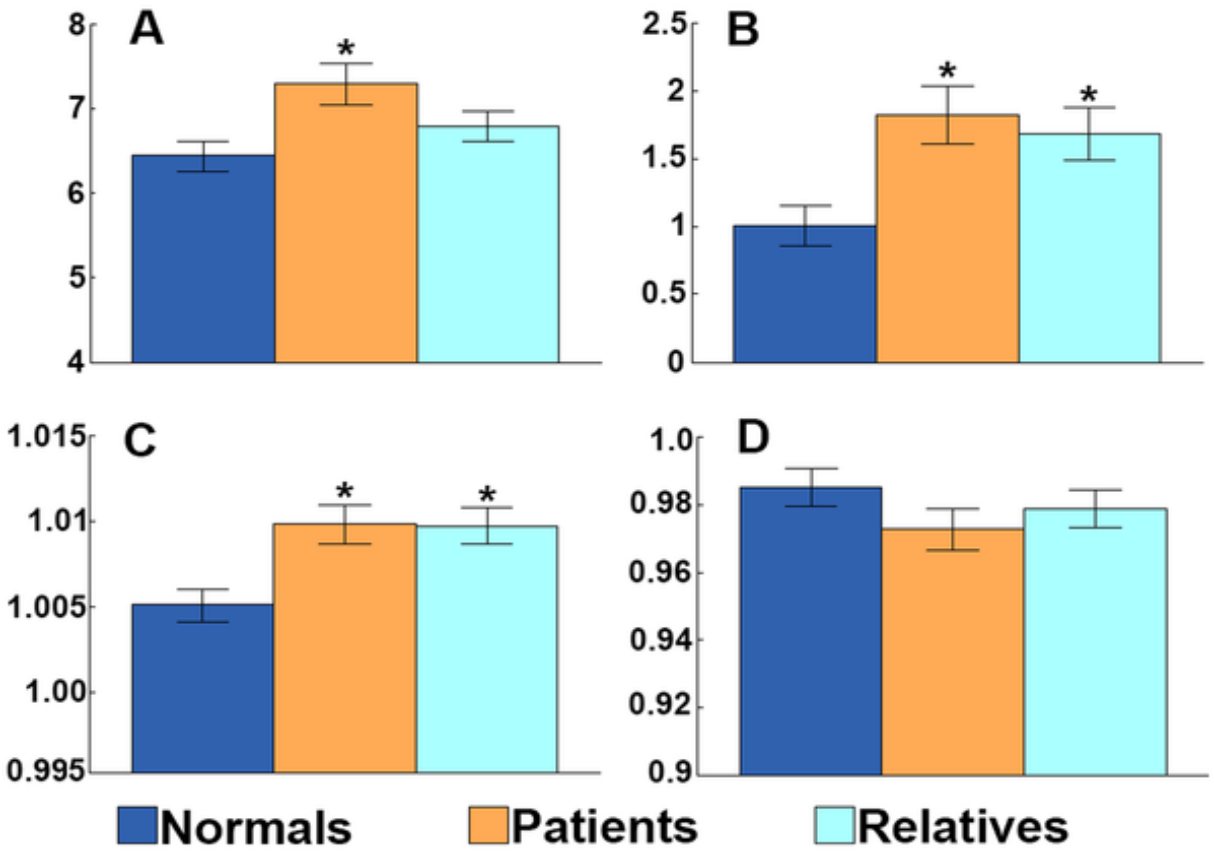


PLOS ONE | 2014; 9(10): e110136.

Revealing a Brain Network Endophenotype in Families with Idiopathic Generalised Epilepsy.

Chowdhury FA, Woldman W, FitzGerald THB, Elwes RDC, Nashef L, Terry JR, Richardson MP.

An abnormal EEG network topology is present in **IGE patients** and **first-degree relatives**.



(A) mean degree *K*, (B) mean degree variance *D*, (C) clustering coefficient , and (D) normalised path length , in the 6–9 Hz band

Conclusioni:

✓Nelle ***epilessie idiopatiche mendeliane,*** le nuove tecniche biomolecolari (GWAS, Exome Sequencing, etc.) consentono di identificare spesso mutazioni non solo di **geni *canale*** ma anche di altri **geni "*non-canale*"** (*DEPDC5, LGI1, PPRT2*, etc.).

✓Molto più difficile e complessa è l'identificazione dei fattori genetici coinvolti nelle **epilessie sporadiche, multifattoriali**, nelle quali sono stati finora identificati svariati loci e/o varianti geniche di incerto significato.

✓Il **link tra deficit molecolare e fenotipo clinico rimane spesso elusivo**, inoltre una considerevole eterogeneità genetica e fenotipica è evidente. Ancora più importante è **l'eterogeneità funzionale dei canali mutati**, indicando una relazione ancora più complessa tra fenotipo clinico e comportamento biofisico del canale.

✓L'estrema eterogeneità genetica e fenotipica suggerisce che differenti meccanismi possono interferire su **specifici network di ipereccitabilità** capace di produrre un determinato fenotipo.

✓L'identificazione di **biomarcatori specifici** è essenziale per la caratterizzazione di network epilettogeni e la comprensione dei meccanismi di epilettogenesi, con possibilità di sviluppare nuovi e affidabili protocolli diagnostici nonché nuove strategie terapeutiche.