Genetics of common forms of epilepsy: approaches and pitfalls

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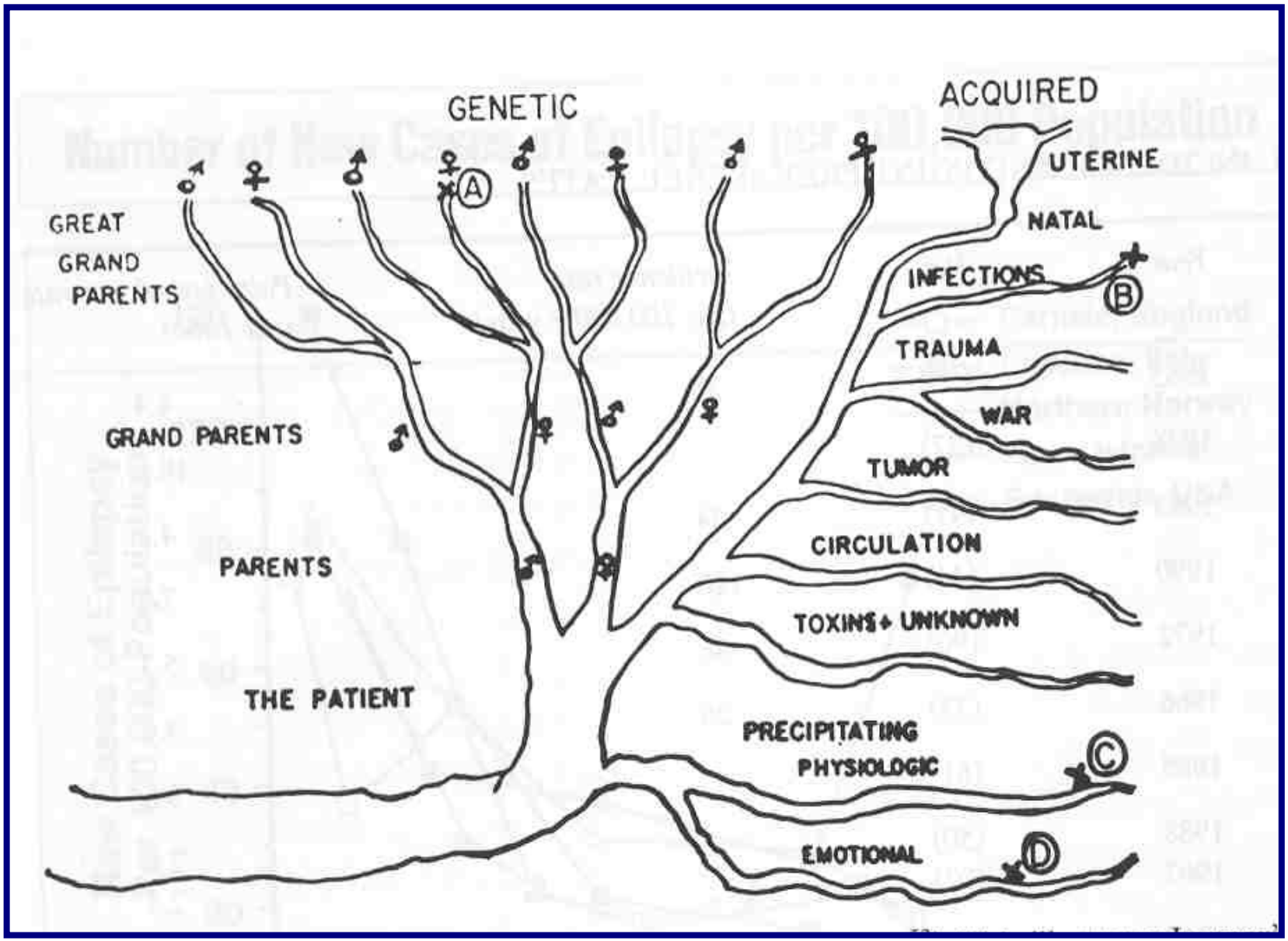
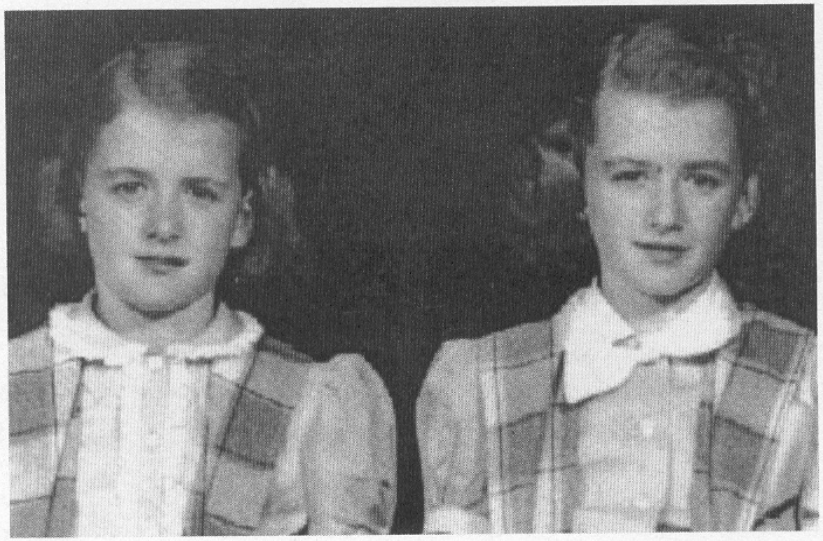


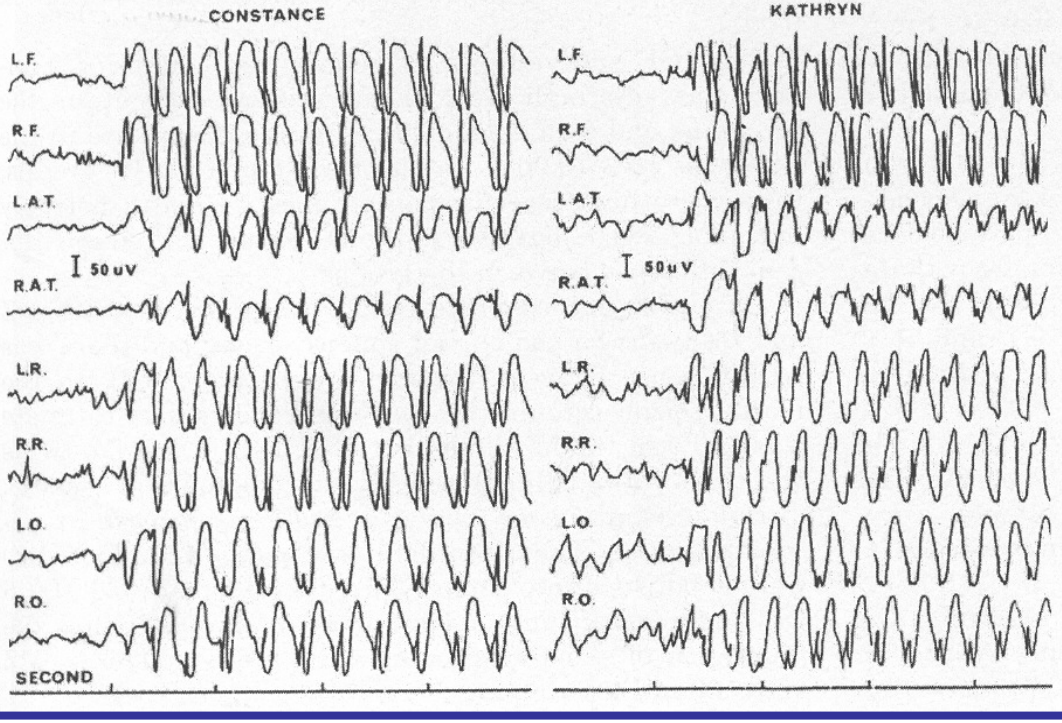
From W Lennox 1960

TABLE 4. *Epilepsy syndromes and related conditions*

- Benign familial neonatal seizures
- Early myoclonic encephalopathy
- Ohtahara syndrome
- [a]Migrating partial seizures of infancy
- West syndrome
- Benign myoclonic epilepsy in infancy
- Benign familial infantile seizures
- Benign infantile seizures (nonfamilial)
- Dravet's syndrome
- HH syndrome
- [a]Myoclonic status in nonprogressive encephalopathies
- Benign childhood epilepsy with centrotemporal spikes
- Early-onset benign childhood occipital epilepsy (Panayiotopoulos type)
- Late-onset childhood occipital epilepsy (Gastaut type)
- Epilepsy with myoclonic absences
- Epilepsy with myoclonic–astatic seizures
- Lennox–Gastaut syndrome
- Landau–Kleffner syndrome (LKS)
- Epilepsy with continuous spike-and-waves during slow-wave sleep (other than LKS)
- Childhood absence epilepsy
- Progressive myoclonus epilepsies
- Idiopathic generalized epilepsies with variable phenotypes
  - Juvenile absence epilepsy
  - Juvenile myoclonic epilepsy
  - Epilepsy with generalized tonic–clonic seizures only
- Reflex epilepsies
  - Idiopathic photosensitive occipital lobe epilepsy
  - Other visual sensitive epilepsies
  - Primary reading epilepsy
  - Startle epilepsy
- Autosomal dominant nocturnal frontal lobe epilepsy
- Familial temporal lobe epilepsies
- [a]Generalized epilepsies with febrile seizures plus
- [a]Familial focal epilepsy with variable foci
- Symptomatic (or probably symptomatic) focal epilepsies
  - Limbic epilepsies
    - Mesial temporal lobe epilepsy with hippocampal sclerosis
    - Mesial temporal lobe epilepsy defined by specific etiologies
    - Other types defined by location and etiology
  - Neocortical epilepsies
    - Rasmussen syndrome
    - Other types defined by location and etiology
- Conditions with epileptic seizures that do not require a diagnosis of epilepsy
  - Benign neonatal seizures
  - Febrile seizures
  - Reflex seizures
  - Alcohol-withdrawal seizures
  - Drug or other chemically induced seizures
  - Immediate and early posttraumatic seizures
  - Single seizures or isolated clusters of seizures
  - Rarely repeated seizures (oligoepilepsy)

[a] Syndromes in development.




CONSTANCE
KATHRYN
L.F.
R.F.
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I 50uV
R.A.T.
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L.O.
R.O.
SECOND

Epilepsies in Twins: Genetics of the Major Epilepsy Syndromes

Samuel F. Berkovic, MD, FRACP,* R. Anne Howell, MSc,* David A. Hay, PhD,† and John L. Hopper, PhD‡

Ann Neurol 1998;43:435–445

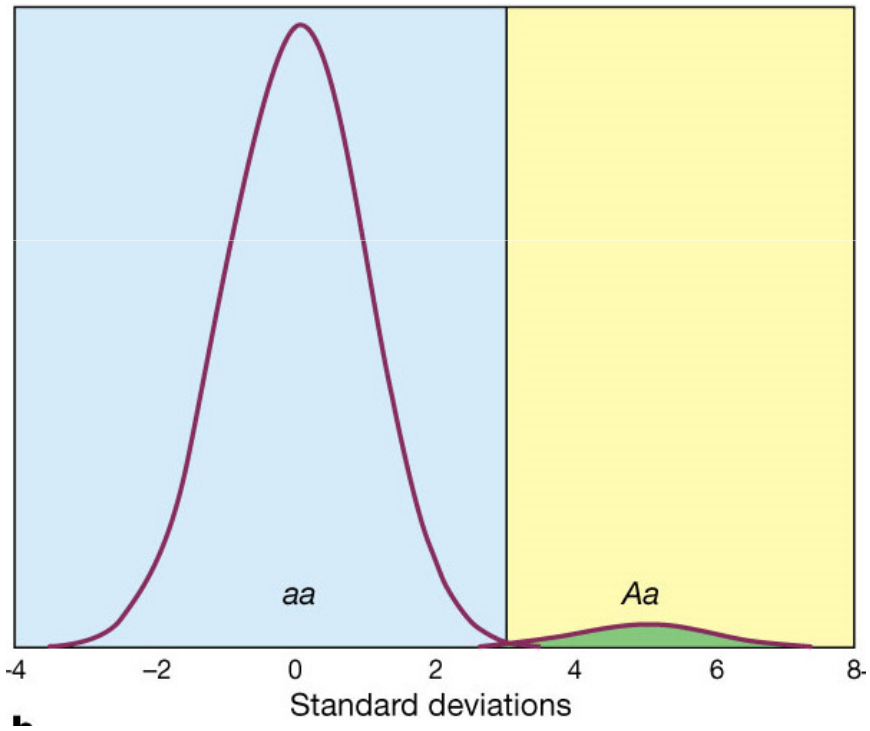
Table 6. Casewise Concordance (±SE) for Major Epilepsy Syndromes in Monozygous and Dizygous Twin Pairs

Epilepsy Syndrome	Pairs	MZ	DZ	*p* Value[a]
All generalized	59	0.82 ± 0.06	0.26 ± 0.11	<0.001
Idiopathic generalized	41	0.76 ± 0.08	0.33 ± 0.12	<0.01
Symptomatic generalized	13	0.83 ± 0.12	0	<0.001
Unclassified generalized	5	1.0	0	—
All partial	65	0.36 ± 0.11	0.05 ± 0.05	0.01
Idiopathic partial	10	0.33 ± 0.25	0.33 ± 0.25	1.0
Cryptogenic	30	0.55 ± 0.14	0	<0.001
Symptomatic partial	25	0	0	—
Special syndromes				
Febrile seizures	82	0.58 ± 0.10	0.14 ± 0.06	<0.001
Neonatal seizures	11	0.67 ± 0.22	0	<0.01
Others	8	0	0	—
Unclassified epilepsies	21	0.53 ± 0.16	0.18 ± 0.16	>0.10

[a]Significance of difference in concordance between monozygous (MZ) and dizygous (DZ) pairs.

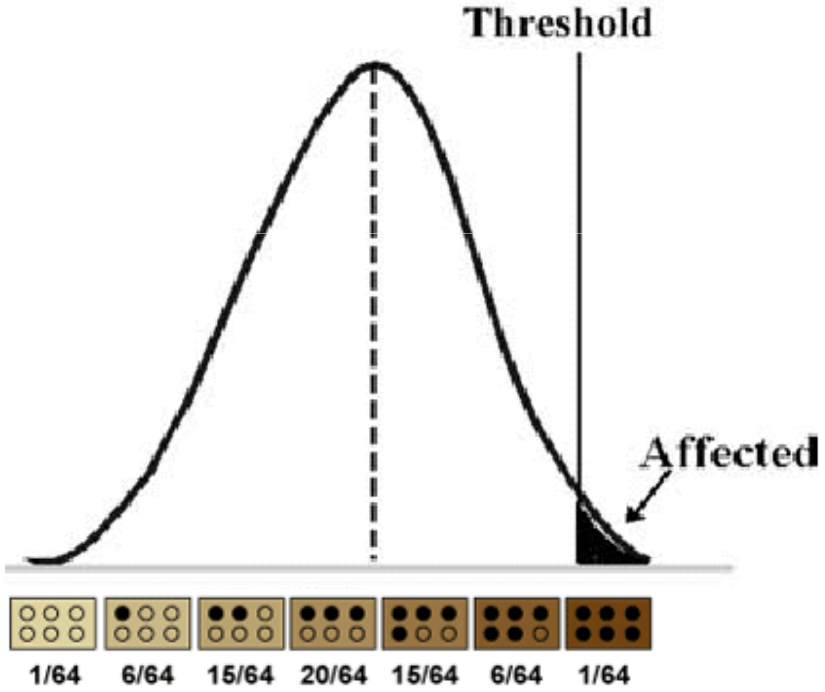
Monogenic inheritance

Mendelian traits



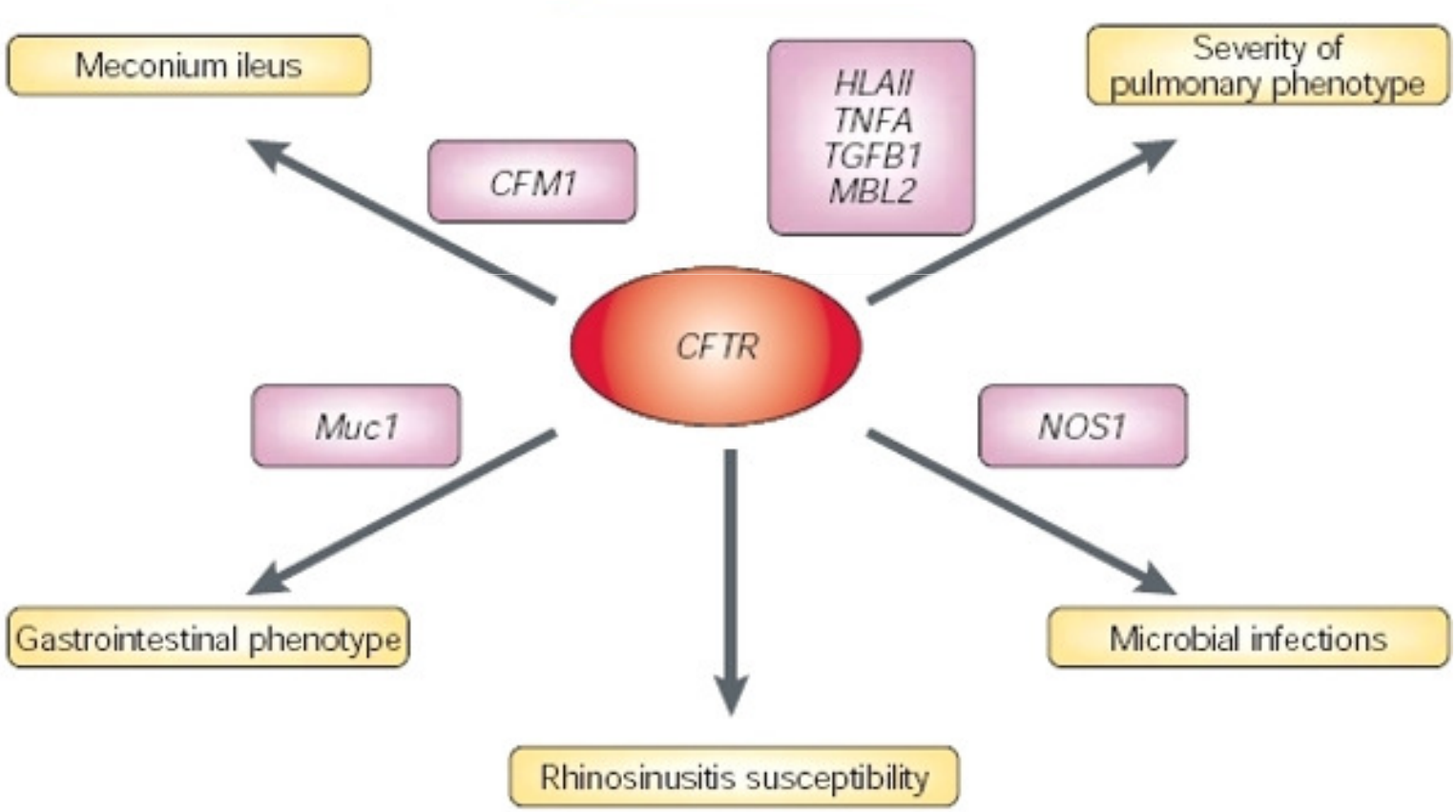
Polygenic inheritance

Complex (discontinuous) traits

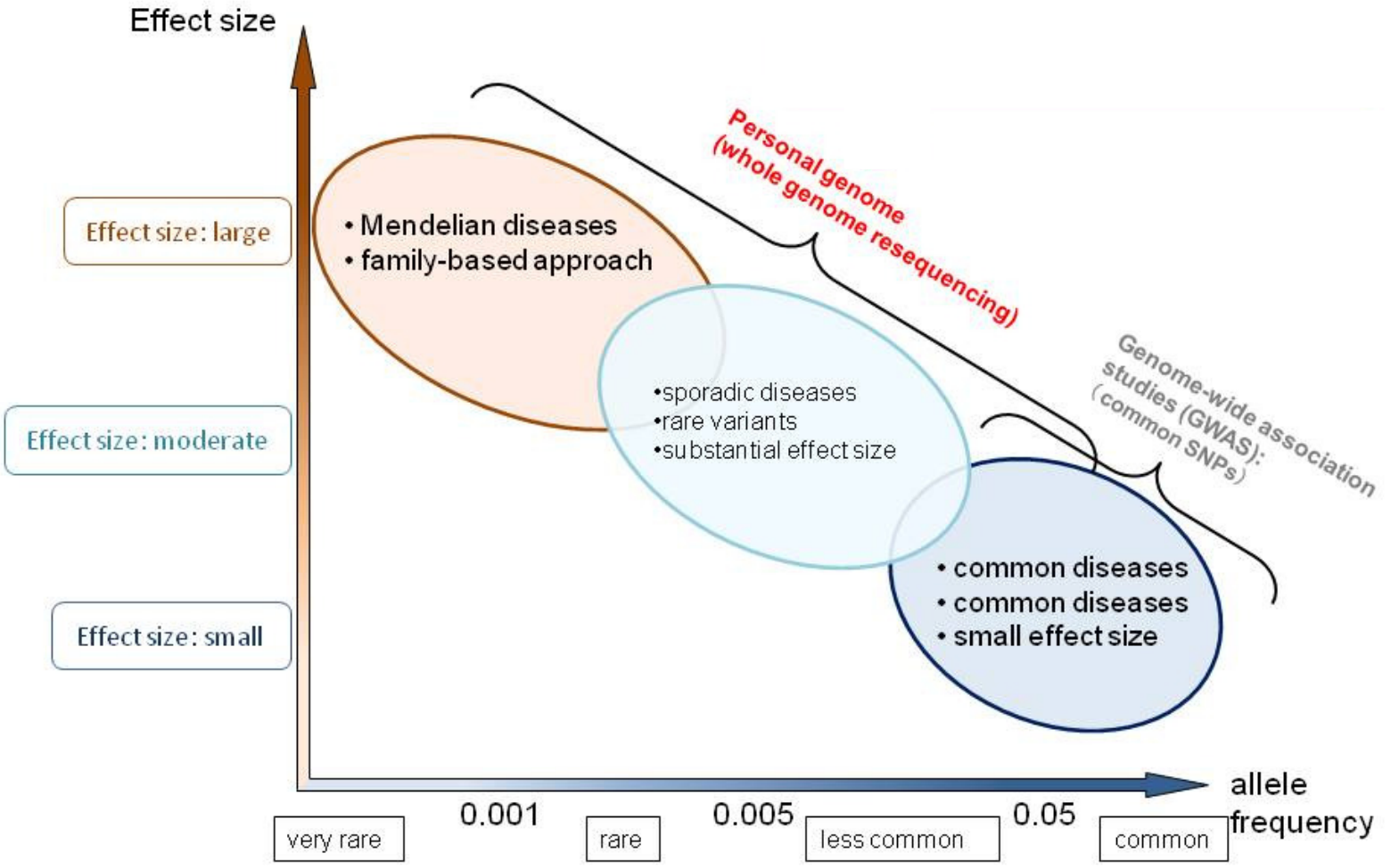


Oligogenic inheritance

Familial traits – sporadic cases

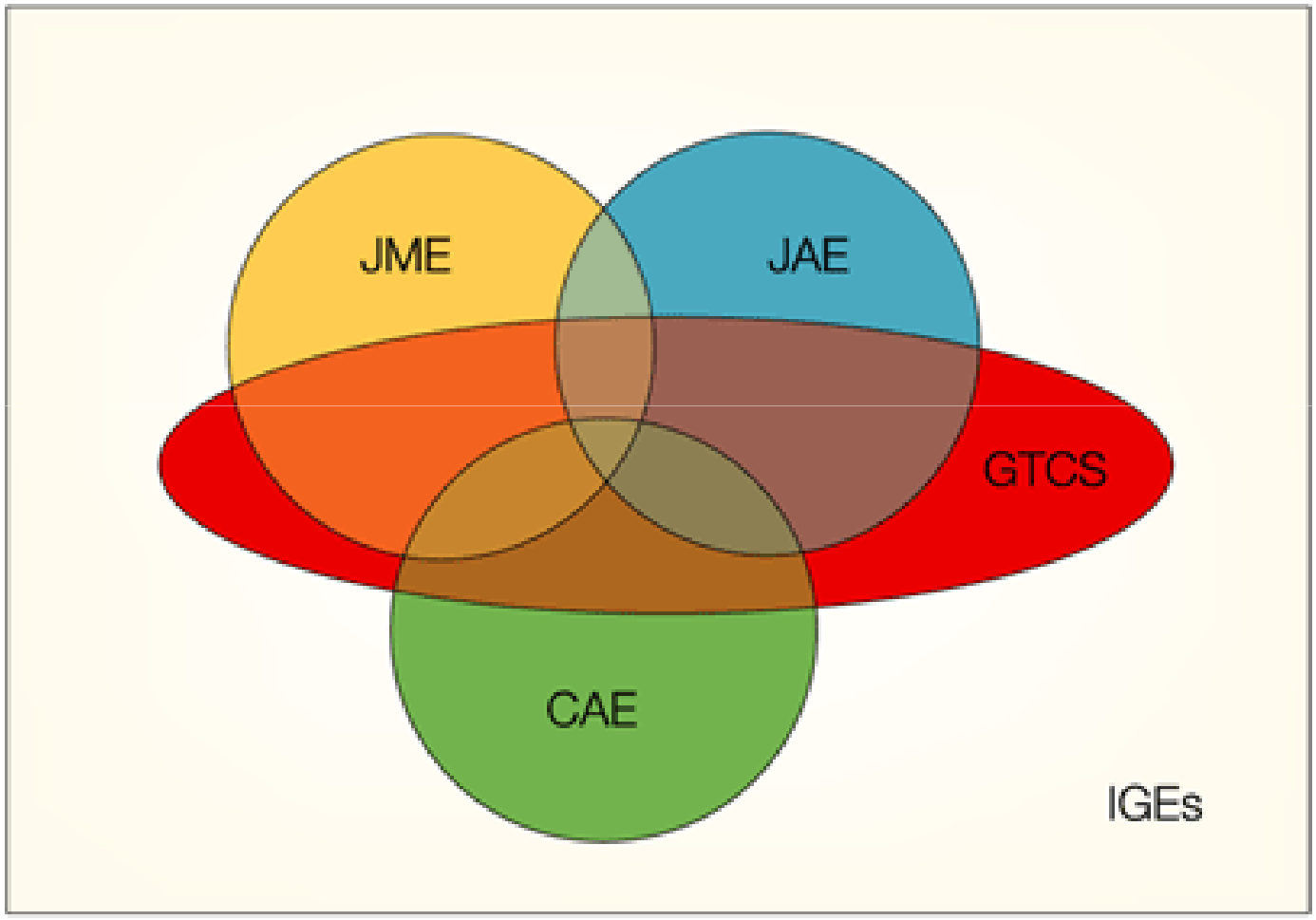


Research paradigm to identify disease-related variations based on comparison of effect sizes of variants and allele frequencies of variants in population.

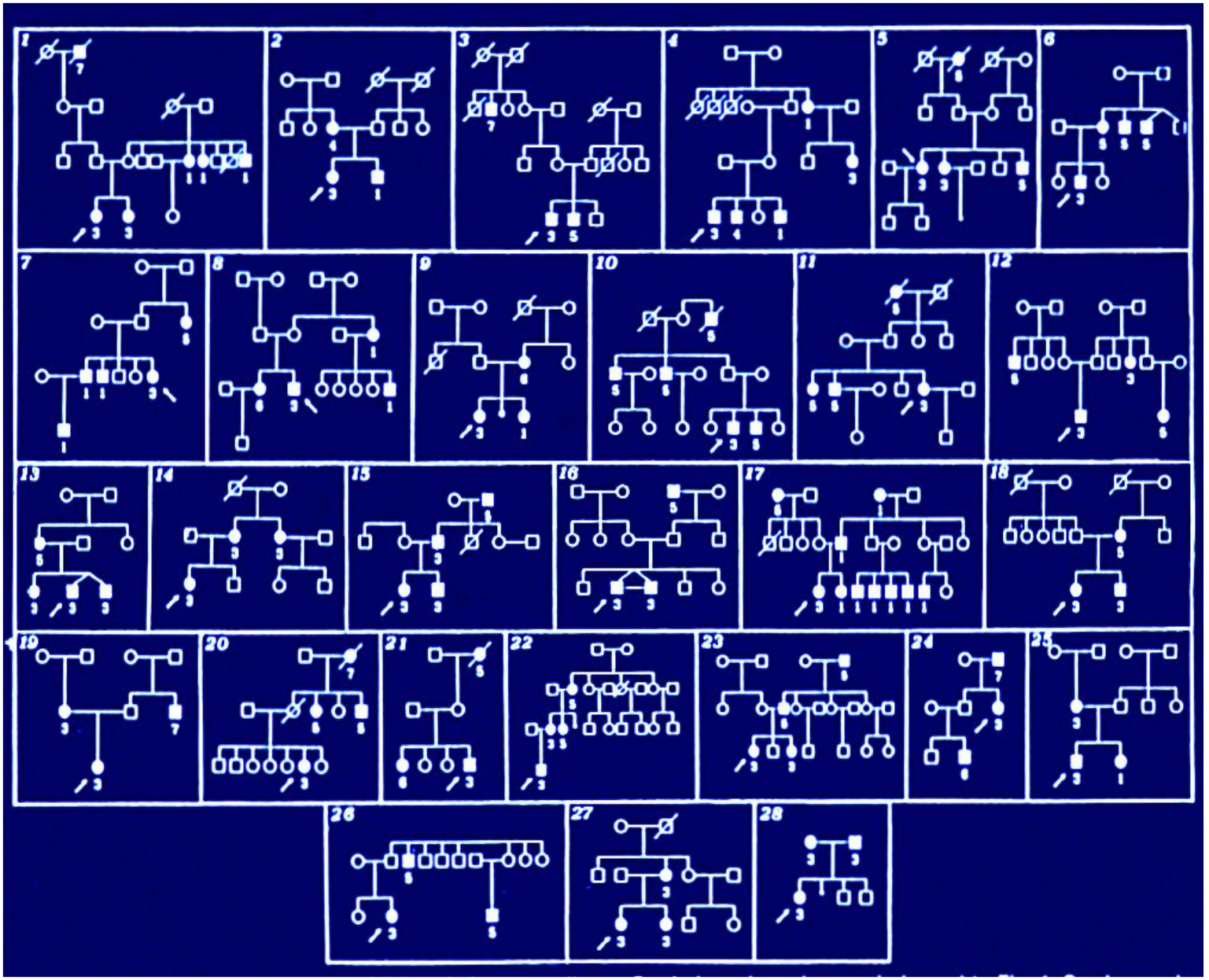


S. Tsuji *Hum. Mol. Genet* (2010)

Idiopathic Generalized Epilepsies

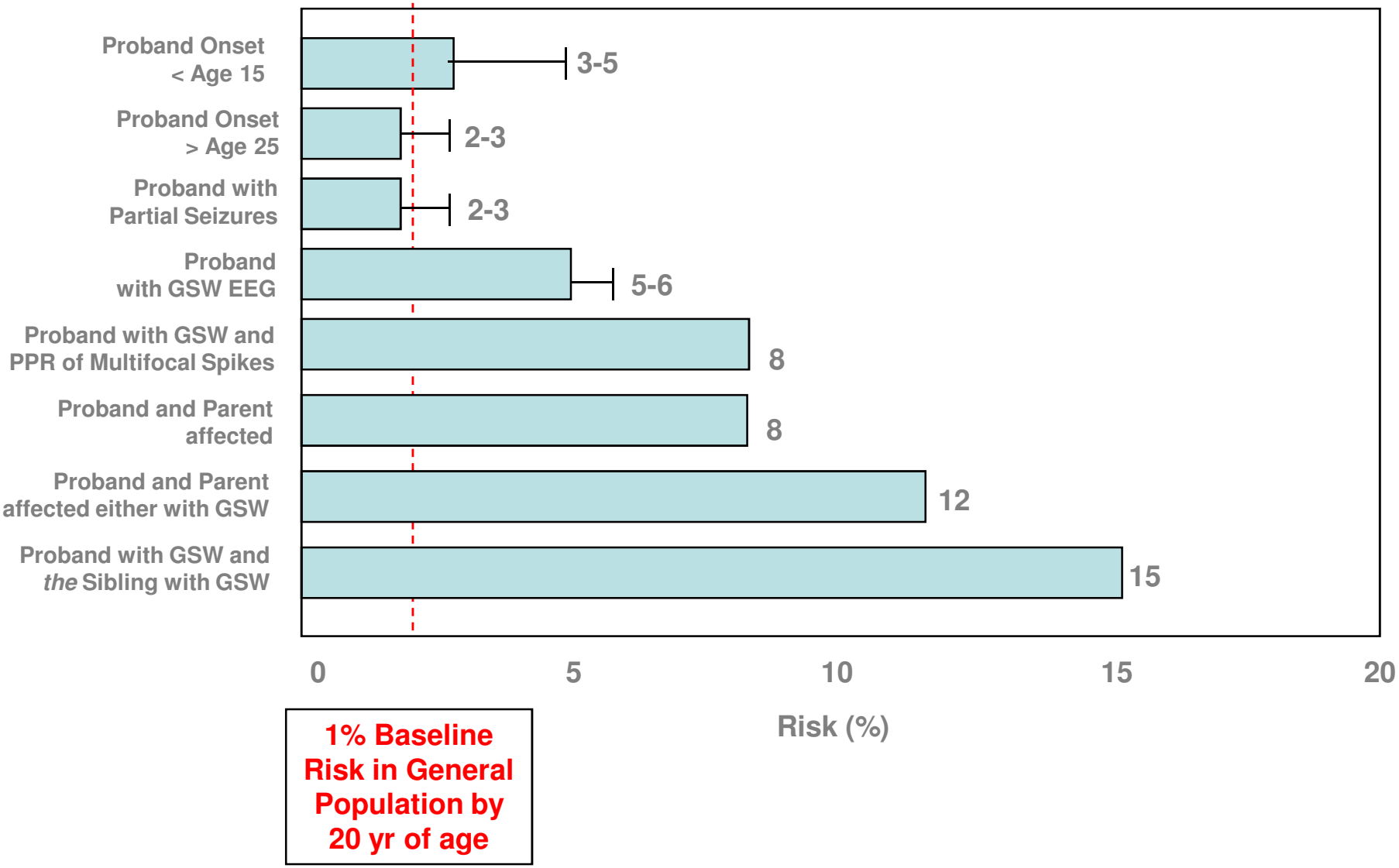


Genetic architecture of IGE



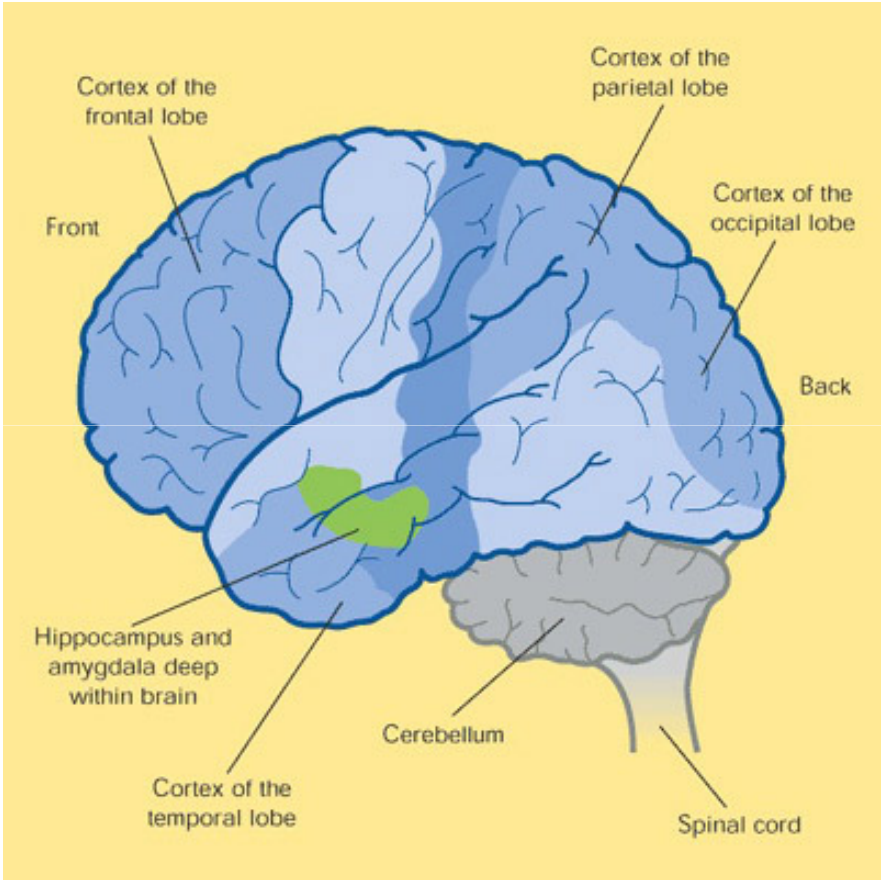
Sibling Risk for Epilepsy

Hauser et al 1990



Temporal lobe epilepsies

- **Hippocampus-amigdala (mesial)**
- **Temporopolar region**
- **Dorsolateral region**



Genetics of temporal lobe epilepsy

L Vadlamudi, I E Scheffer, S F Berkovic

Our traditional understanding is that TLE is an acquired condition, but only now are we beginning to understand the extent of genetic involvement

Table 1 Familial temporal lobe epilepsy (TLE) subtypes

		Familial mesial (FM) TLE syndromes*			TLE in broader partial epilepsy syndromes syndrome	
Syndrome	**ADPEAF**[7–11]	**FMTLE no HS no FS**[16–20]	**FMTLE often HS +/−FS**[22 23]	**FMTLE with FS usually no HS**[27 28]	**FPEVF**[32 33]	**PEPS**[34]
Typical age of onset†	8 years to 4th decade	10 years to 4th decade	1 year to 3rd decade	1 year to 2nd decade	1 year to 4th decade	2 years to 2nd decade
Characteristic features	Auditory, sensory aura	Psychic, autonomic aura			Seizures with different focal origin in family members	Multiple seizure types in the same individual
EEG	Rare temporal discharges	Rare temporal discharges	Frequent temporal discharges	Occasional temporal discharges	Occasional temporal discharges	Frequent peri-central spikes
MRI	Normal	Normal	HS	Normal	Normal	Normal
Outcome	Generally benign	Generally benign	Often refractory	Variable	Variable	Generally benign
Linkage	10q		–	18qt,1q (?)	22q,2q (?)	4p
Genes	LGI1	–	–	–	–	–

*These divisions are preliminary and they are probably overlapping mesial TLE syndromes. †Range of onset ages reflects the majority of reported cases. Some ''outliers'' may begin earlier or later, but most family members fall within the stated ranges.
ADPEAF, autosomal dominant partial epilepsy with auditory features; HS, hippocampal sclerosis; FS, febrile seizures; FPEVF, familial partial epilepsy with variable foci; PEPS, partial epilepsy with pericentral spikes.

J Neurol Neurosurg Psychiatry
2003;**74**:1359–1361

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

Douglas E. Crompton,[1,2,3] Ingrid E. Scheffer,[1,4] Isabella Taylor,[5] Mark J. Cook,[6] Penelope A. McKelvie,[7] Danya F. Vears,[1] Kate M. Lawrence,[1] Jacinta M. McMahon,[1] Bronwyn E. Grinton,[1] Anne M. McIntosh[1] and Samuel F. Berkovic[1]

Model A = TLE, AD, 80% penetrance
Model B = TLE, AD, 60% pentrance
Model C = All Epilepsies, AD, 80% penetrance
Model D = All Epilepsies, AD 60% penetrance

Table 3 Segregation of temporal lobe epilepsy and other epilepsies

Family set	Model	Eligible relatives[a]	Relatives with TLE	Relatives with other epilepsy	Expected number of affected relatives	*P*-value (accept model)
Monozygotic twin families	A	64	4	NA	25.6	1.5×10^{-9}
	B	64	4	NA	19.2	6.6×10^{-6}
	C	65	4	5	25.6	5.9×10^{-6}
	D	65	4	5	19.5	0.0041
Non-twin families	A	266	45	NA	106.4	5.1×10^{-16}
	B	266	45	NA	79.8	1.2×10^{-6}
	C	266	45	19	106.4	5.6×10^{-8}
	D	266	45	19	79.8	0.038
Combined families	A	330	49	NA	132	$<2.2 \times 10^{-16}$
	B	330	49	NA	99	1.9×10^{-10}
	C	331	49	24	132.4	6.4×10^{-12}
	D	331	49	24	99.3	0.0014

a First-degree relatives and antecedent second-degree relatives from affected side of family are combined (see 'Patients and methods' section). These non-temporal lobe epilepsy individuals are not considered under Models A and B. NA = not applicable; TLE = temporal lobe epilepsy.

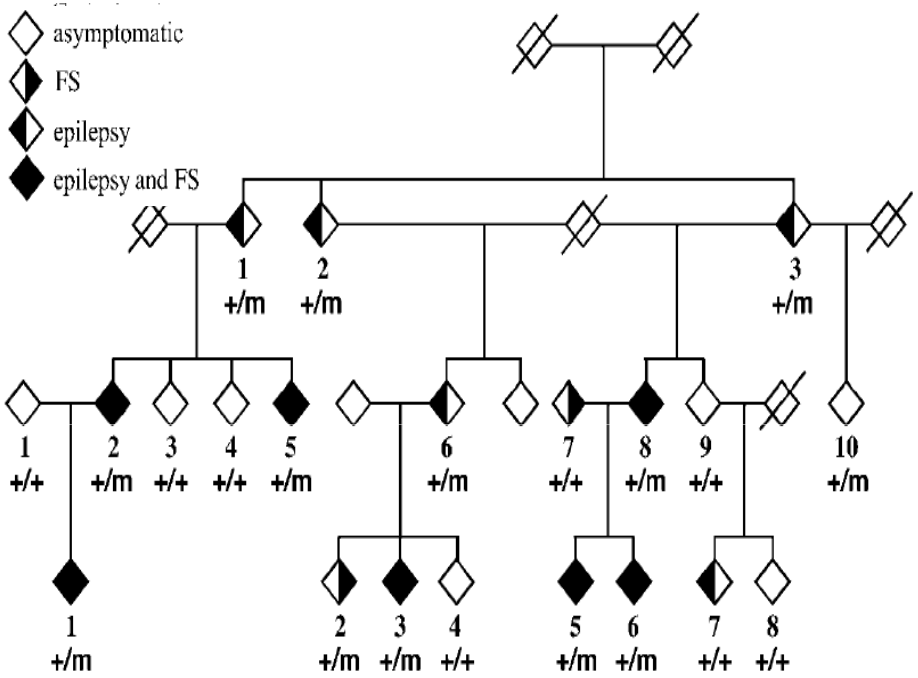
Rare penetrant alleles
-
Familial traits

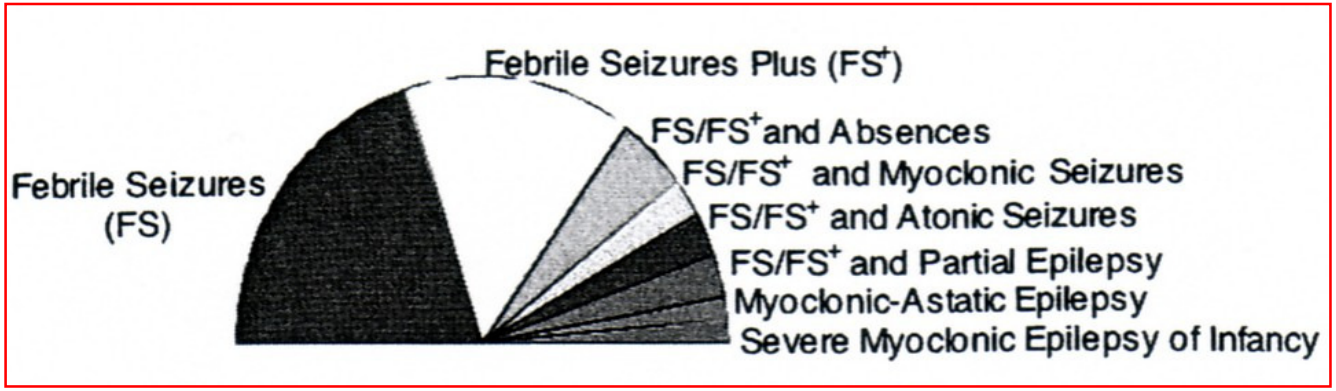
Generalized Epilepsy and Febrile Seizures plus

Clinical features

- Clinical Variability
- Febrile Seizures (< 6 y)
- Febrile Seizures "plus" (> 6y)
- Afebrile seizures, usually generalized (tonic-clonic, absence, myoclonic, atonic)
- Benign outcome
- No brain lesions or metabolic disorders

Genetic features



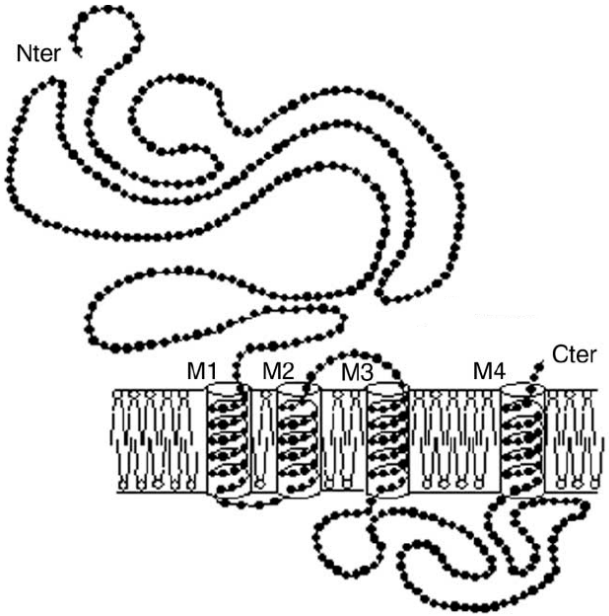


Generalized epilepsy with febrile convulsions plus

GABRG2

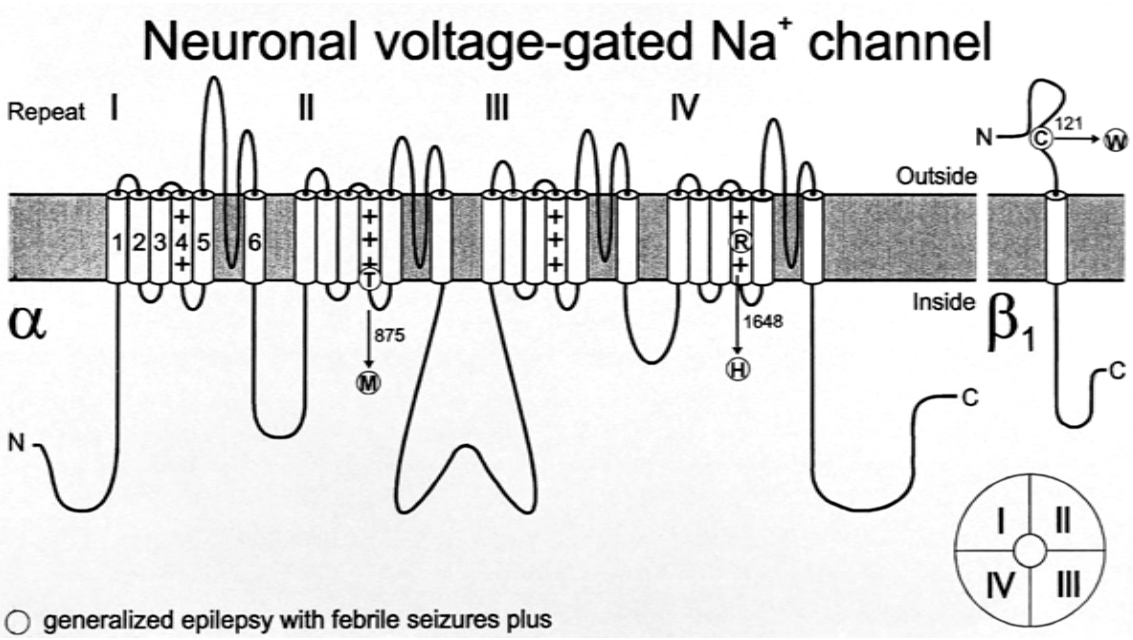
$GABA_A$ receptor

γ_2 subunit



SCN1A – SCN1B

Voltage-gated Na+ channel subunits



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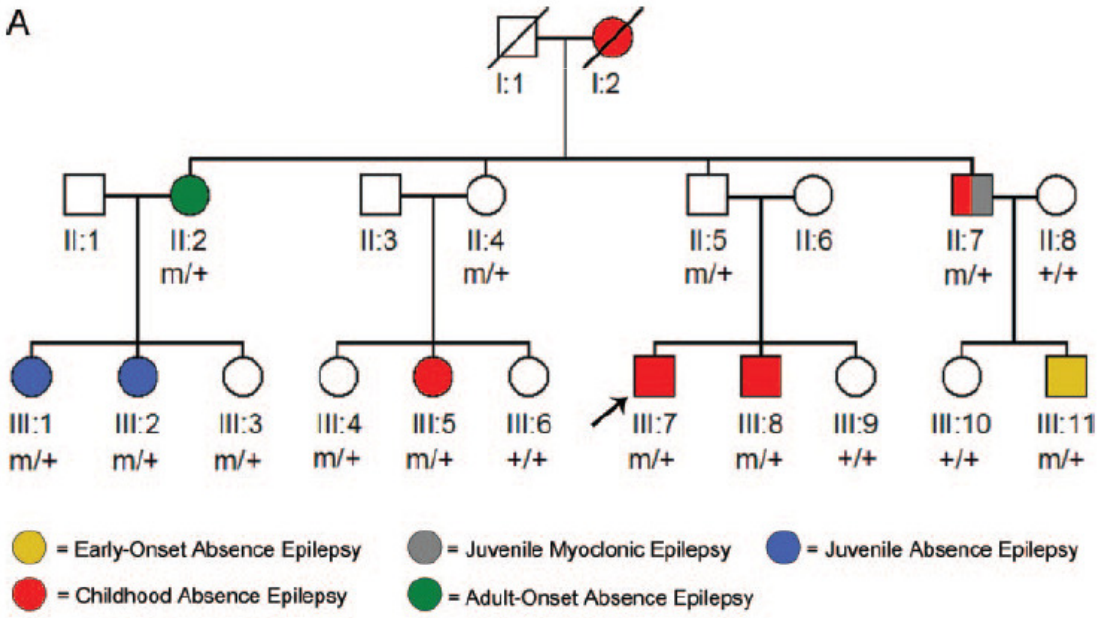
C. Marini, MD, PhD
On behalf of the
EPICURE
Consortium

GLUT1 mutations are a rare cause of familial idiopathic generalized epilepsy

Neurology® 2012;78:557–562

Figure 1 Pedigree of the idiopathic generalized epilepsies (IGE) family carrying the *SLC2A1* mutation and evolutionary conservation of the mutated residue



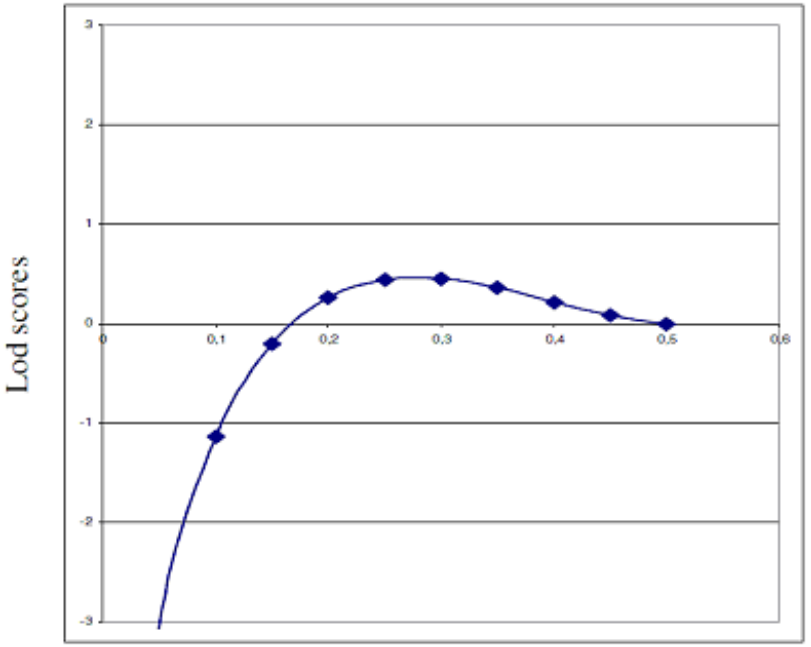
Screening of 66 ion channel genes in 95 families with IGE (at least three affected cases per family)

Unreported nonsynonymous variants (dbSNP132)(< 1% in 760 caucasian controls)			
N° Variants	N° genes with variants	Families	Segregation
70	35	82	60

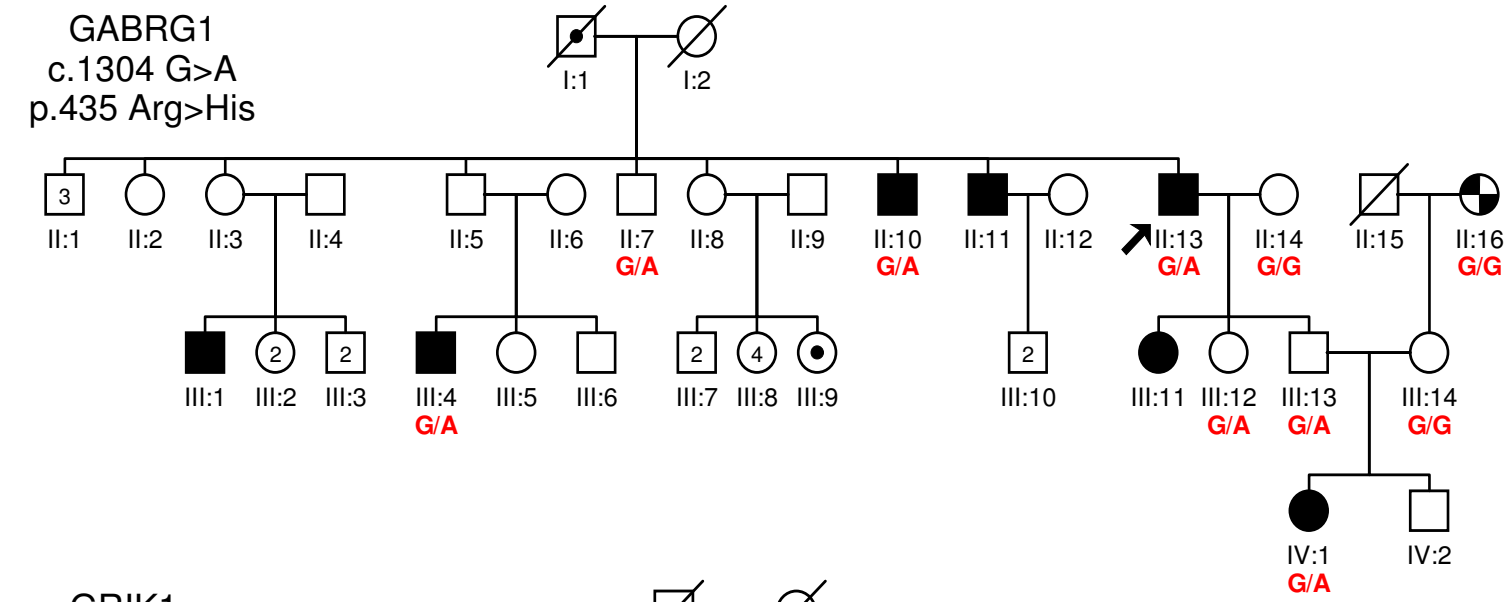
Linkage analysis assuming

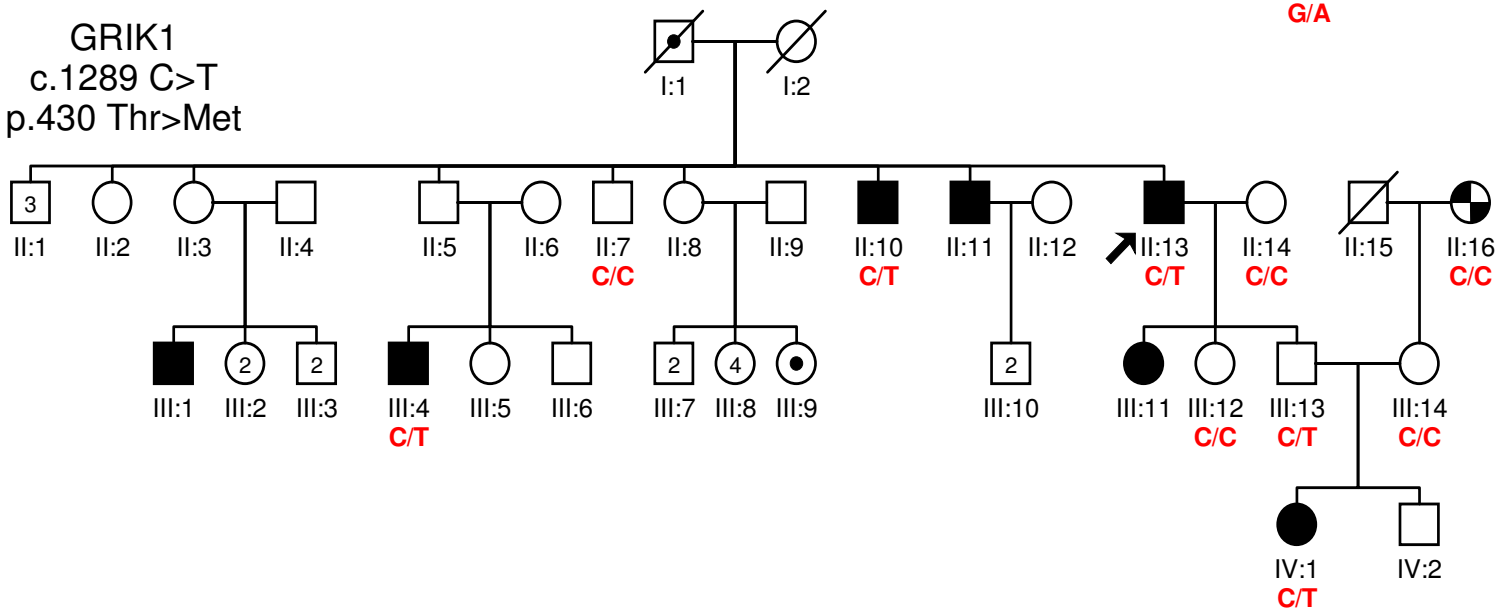
an autosomal dominat model

with reduced penetrance

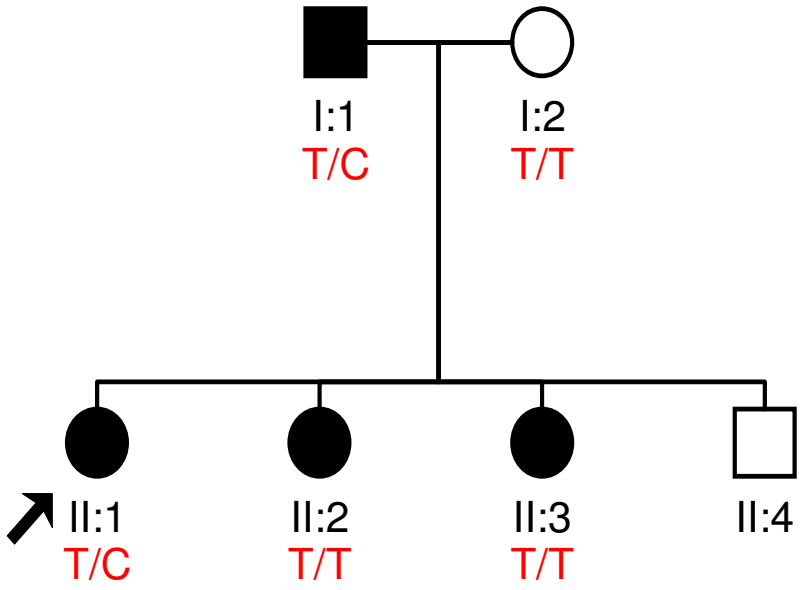


- Segregation analysis perfomed for 70 variants





SCN11A
c.3473 T>C
p.Leu1158Pro



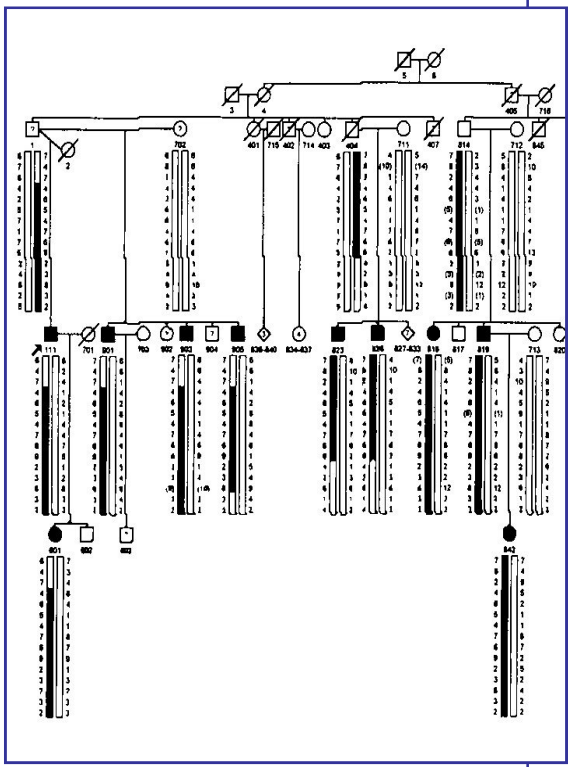
Preliminary conclusions

- allelic diversity
- low clustering of rare variants in individual genes
- most variants do not segregate
- cosegregation may be casual

Mutations in *LGI1* cause autosomal-dominant partial epilepsy with auditory features

Sergey Kalachikov[1], Oleg Evgrafov[1], Barbara Ross[1], Melodie Winawer[2,5], Christie Barker-Cummings[2,3], Filippo Martinelli Boneschi[2,3], Chang Choi[9], Pavel Morozov[1], Kamna Das[1], Elita Teplitskaya[1], Andrew Yu[1], Eftihia Cayanis[1], Graciela Penchaszadeh[1,4,8], Andreas H. Kottmann[9], Timothy A. Pedley[5], W. Allen Hauser[2,3,5], Ruth Ottman[2,3,7] & T. Conrad Gilliam[1,4,6,8]

Published online: 28 January 2002, DOI: 10.1038/ng832



rmation used for diagnosis in subjects with seizures

		rmation	EEG	Neurological examination	Age at onset	Seizure classifications[a] (aetiology)
			Yes	Yes	8	SP, SGTC, auditory features
601	Self, father		Yes	Yes	12	SP (possible), CP, SGTC, auditory features
816	Brother, son, daughter, spouse[b]		No	No	16	CP, SGTC
818	Self, mother, father		No	No	12	SGTC
819	Self, mother, father		No	Yes	13	CP, SGTC, auditory features
823	Self, mother, father		Yes	Yes	19	Nocturnal GTC
826	Self, mother, father		Yes	No	12	CP, SGTC
842	Self, mother		Yes	Yes	8	CP, SGTC, auditory features
901	Self, mother		Yes	Yes	10	P, SGTC
903	Self, mother		Yes	Yes	12	CP, SGTC, auditory features
905	Self, mother		Yes	Yes	17	P, SGTC, auditory features
Symptomatic epilepsy						
402	Spouse, brother, sister-in-law[b]		No	No	56	P, SGTC (neoplasm)
407	Brother, sister-in-law[b]		No	No	1	Unknown seizure type (cerebral palsy)
902	Self, mother		Yes	Yes	25	SP, SGTC, auditory features (head injury)
Acute symptomatic seizures						
001	Self		Yes	Yes	55	(Alcohol-related seizures)
702	Self		No	No	2	(Febrile convulsion)
904	Self, mother		No	No	1	(Febrile convulsions) (2)
Epilepsy possible but uncertain						
405	Two sons[b]		No	No	?	unknown
802	Mother		No	No	4	SP

[a]Seizure types: SP, simple partial; CP, complex partial; SGTC, secondarily generalized tonic-clonic; GTC, generalized tonic-clonic; P, partial, unknown whether simple or complex.
[b]Deceased subject.

DOI: 10.1093/brain/awh151 *Brain* (2004), **127**, 1343–1352

Idiopathic partial epilepsy with auditory features (IPEAF): a clinical and genetic study of 53 sporadic cases

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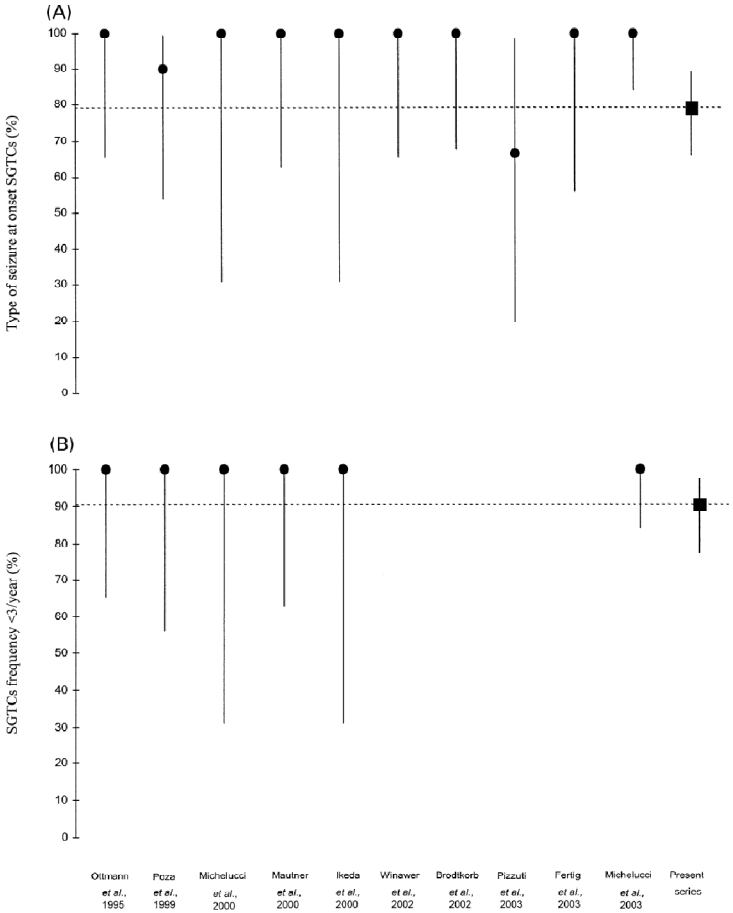
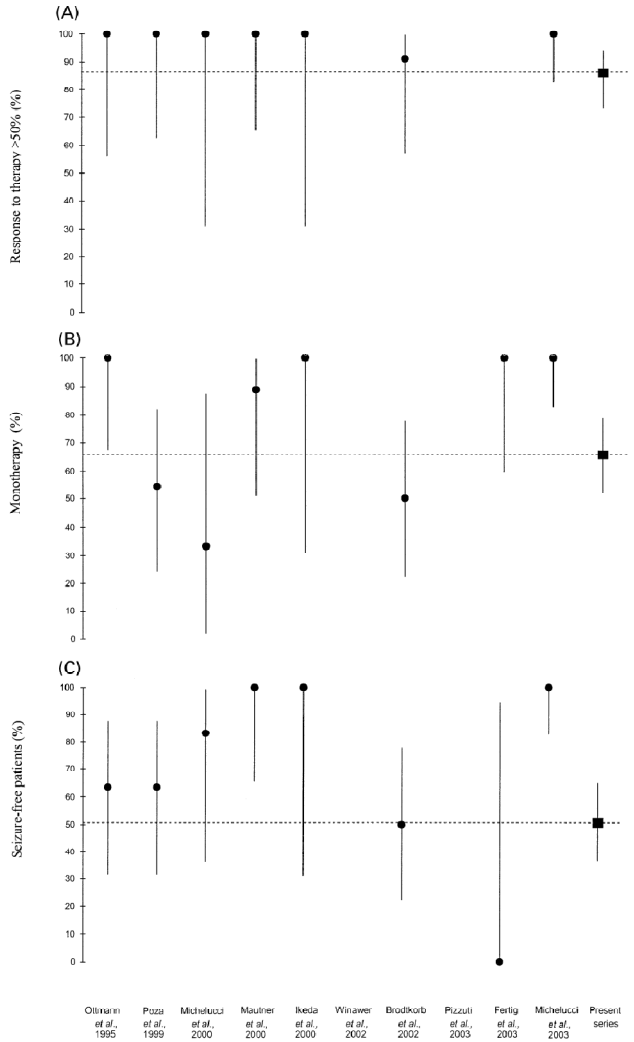
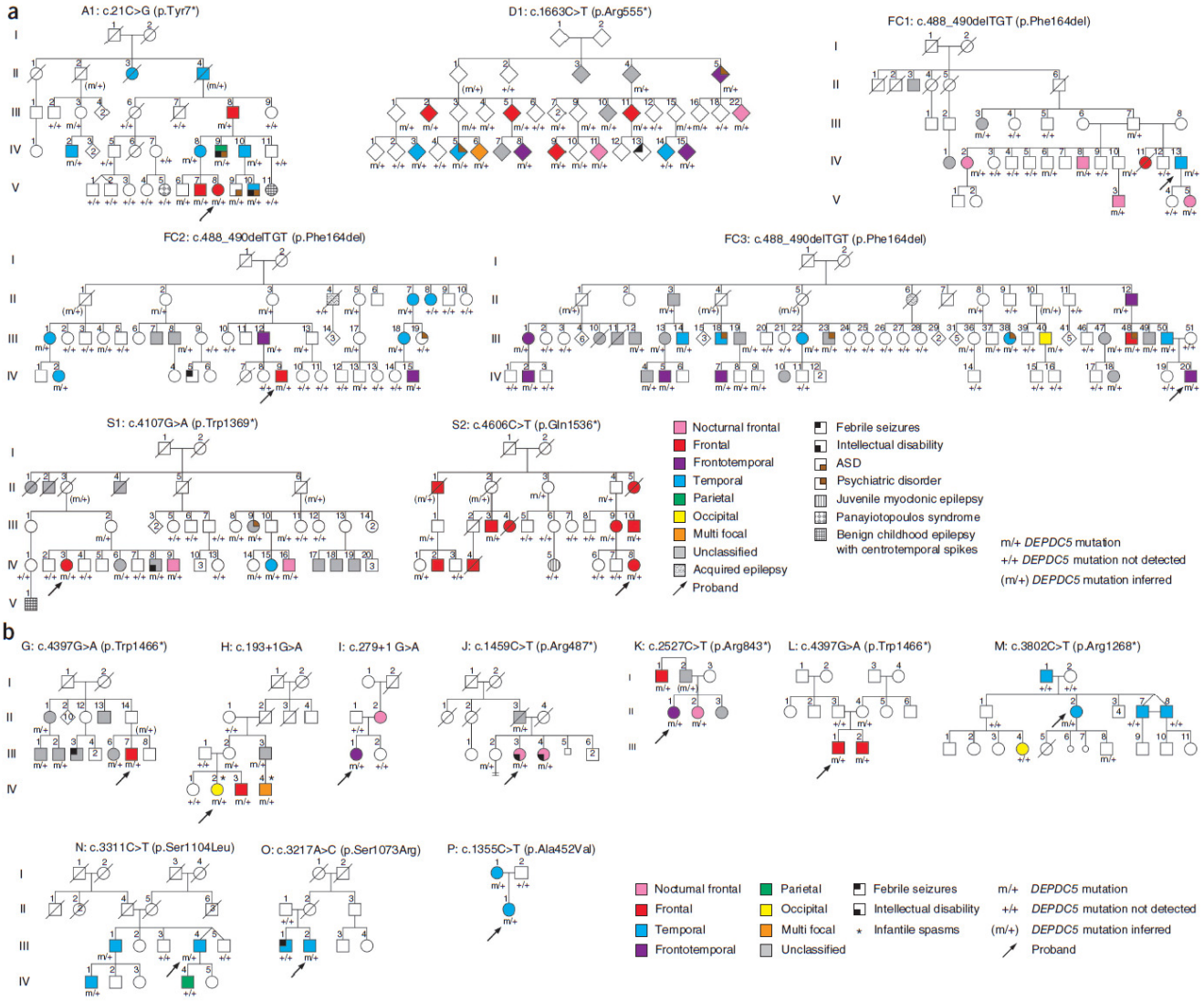




Mutations in *DEPDC5* cause familial focal epilepsy with variable foci

[2], Bree L Hodgson[1], [6], Karl Martin Klein[6,8], ia Iona[1], Brigid M Regan[6], [14], John C Mulley[7,15,16], Q Thomas[7], Jozef Gecz[7,16], M J M van den Maagdenberg[3,20],



Mutations in Mammalian Target of Rapamycin Regulator *DEPDC5* Cause Focal Epilepsy with Brain Malformations

Ingrid E. Scheffer, MB, BS, PhD,[1,2,3]
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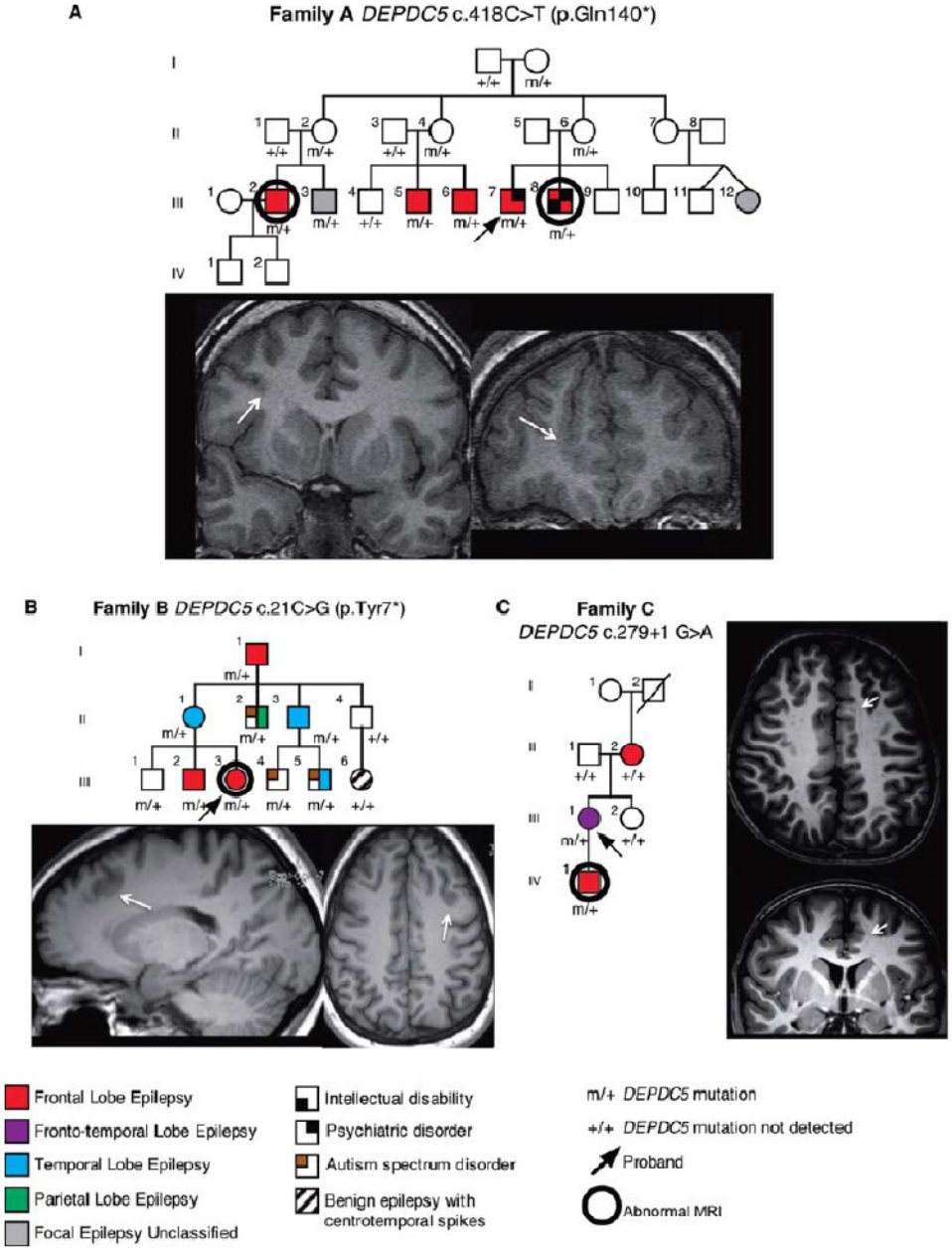
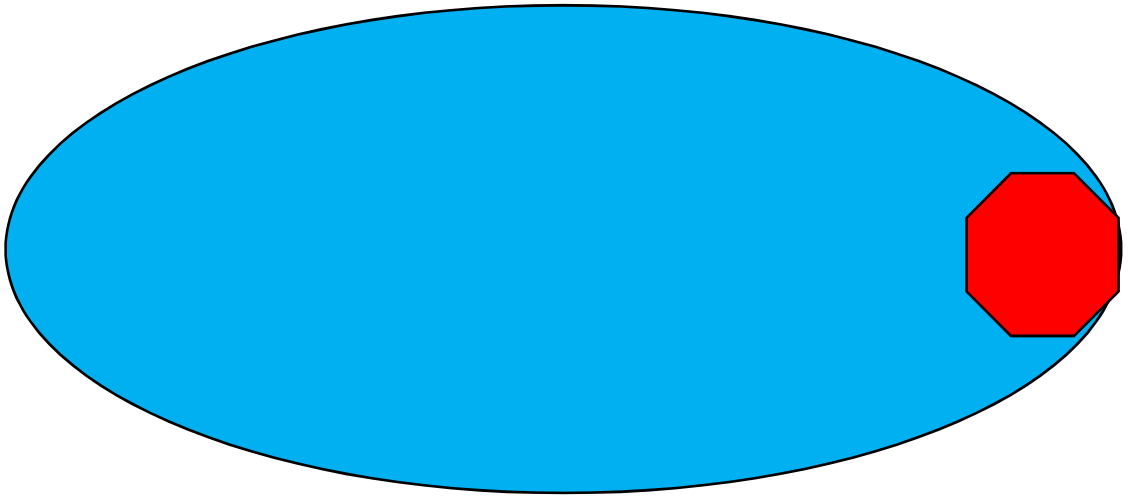
Lata Vadlamudi, MB, BS, PhD,[1,10]
Jozef Gecz, PhD,[11]
Alan Connelly, PhD,[2,12]
Paolo Tinuper, MD,[8,9]
Michael G. Ricos, BSc, PhD,[4,5]
Samuel F. Berkovic, MD, FRS,[1] and
Leanne M. Dibbens, BSc, PhD[4,5]



Genetics of the Epilepsies

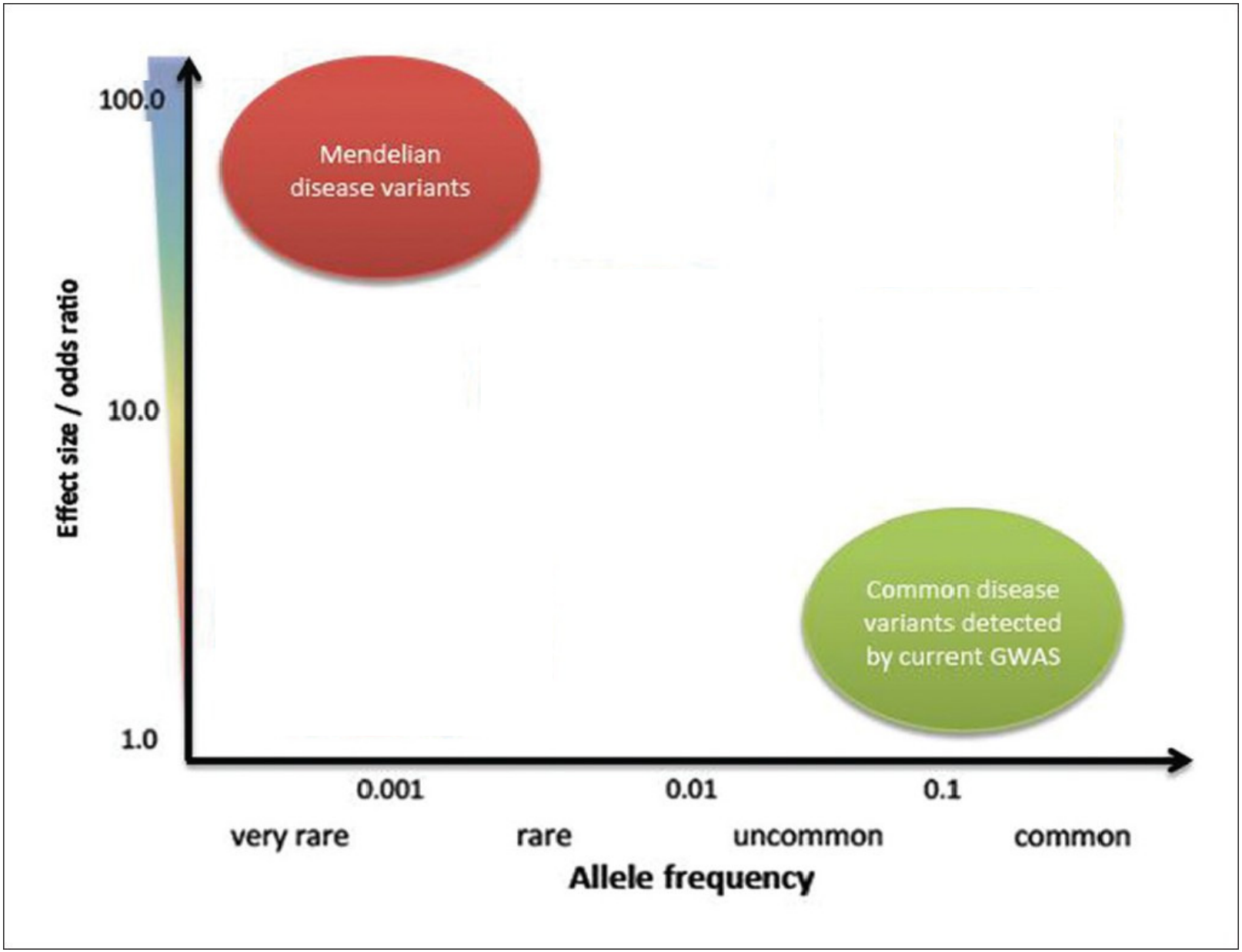
> 95% sporadic cases with Complex inheritance



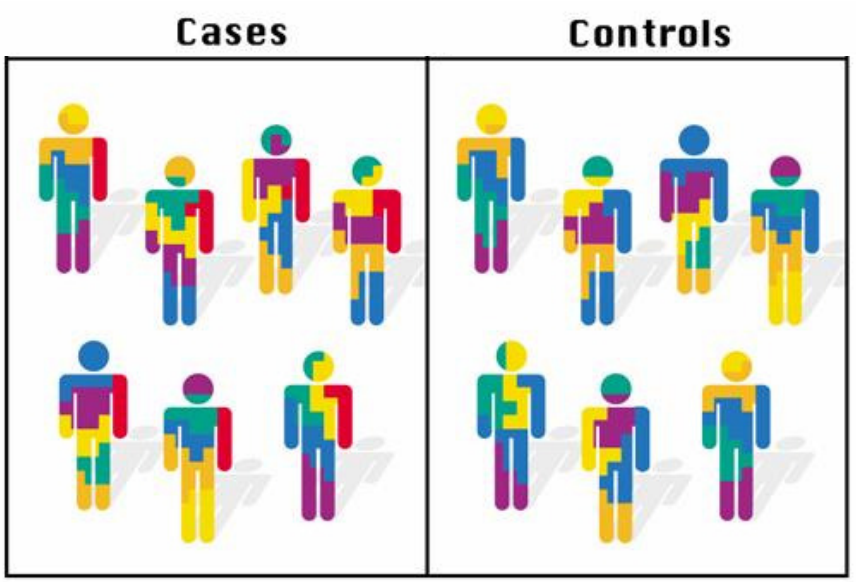
< 5% Families with Monogenic inheritance

Susceptibility genes
–
Common (sporadic) traits

Common Disease – Common Variants Hypothesis



Genome-wide Association Studies



- Copy Number Variations (CNVs)

- Single Nucleotide Polymorphisms (SNPs)

15q13.3 microdeletions increase risk of idiopathic generalized epilepsy

Ingo Helbig[1], Heather C Mefford[2], Andrew J Sharp[3], Michel Guipponi[3], Marco Fichera[4], Andre Franke[1], Hiltrud Muhle[1], Carolien de Kovel[1], Carl Baker[2], Sarah von Spiczak[1], Katherine L Kron[1], Ines Steinich[1], Ailing A Kleefuß-Lie[1], Costin Leu[1], Verena Gaus[1], Bettina Schmitz[1], Karl M Klein[1], Philipp S Reif[1], Felix Rosenow[1], Yvonne Weber[1], Holger Lerche[1], Fritz Zimprich[1], Lydia Urak[1], Karoline Fuchs[1], Martha Feucht[1], Pierre Genton[5], Pierre Thomas[6], Frank Visscher[1], Gerrit-Jan de Haan[1], Rikke S Møller[1], Helle Hjalgrim[1], Daniela Luciano[4], Michael Wittig[1], Michael Nothnagel[1], Christian E Elger[1], Peter Nürnberg[1], Corrado Romano[4], Alain Malafosse[3], Bobby P C Koeleman[1], Dick Lindhout[1], Ulrich Stephani[1], Stefan Schreiber[1], Evan E Eichler[2,7] & Thomas Sander[1]

Table 2: Recurrent microdeletions in IGE patients and population controls

Chrom. region	Chrom. Position (Mb)	MicroDel Size (Mb)	IGE N = 1104	Controls N = 1723	p-value *
1q21.1	145.0-146.4	1.35	1	0	
15p11.2	20.3-20.75	0.4	12	3	**0.002**
15q13.3	28.7-30.3	1.5	10	0	**8×10^{-5}**
15q24	72.1-73.8	1.7-3.9	0	0	
16p11.2	29.4-30.3	0.6	1	0	
16p13.11	14.7-16.7	1.65	5	1	**0.037**
17q12	31.2-33.85	1.8	0	0	
17q21.31	14.0-14.5	0.5-0.65	0	0	
22q11.2	17.5–20.5	3	2	0	
MicroDels			**31**	**4**	**1.4×10^{-9}**

Table 1: Recurrent microdeletions reported in neuropsychiatric disorders

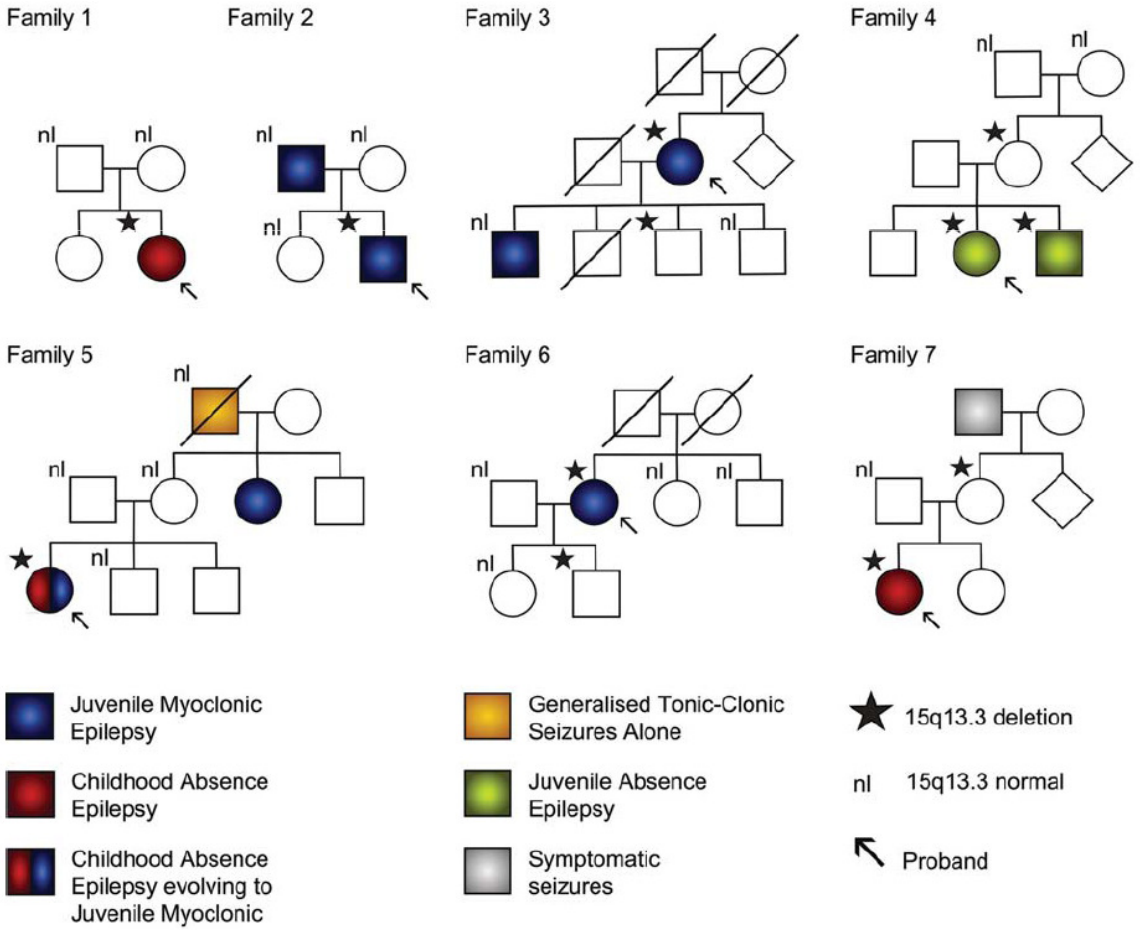
Chrom. segment	Chrom. position (Mb)	MicroDel size (Mb)	Candidate gene	Neuropsychiatric disorder
1q21.1	145.0-146.4	1.35	*GJA8*	ID, ASP, SZ
15p11.2	20.3-20.75	0.4	*CYPIF1*	SZ
15q13.3	28.7-30.3	1.5	*CHRNA7, TRPM1*	ID/EPI, ASP, SZ, PSY
15q24	72.1-73.8	1.7-3.9	*CYP1A1/A2, HCN4*	ID
16p11.2	29.4-30.3	0.6	*KCTD13, SEZ6L2*	ASP
16p13.11	14.7-16.7	1.65	*NDE1*	ID
17q12	31.2-33.85	1.8	*TCF2*	EPI
17q21.13	14.0-14.5	0.5-0.65	*MAPT, CRHR1*	ID
22q11.2	17.5–20.5	3	*COMT, SNAP29*	SZ

ASP: autism spectrum disorder; EPI: epilepsy, ID: intellectual disability, SZ: schizophrenia, PSY: psychotic disorders

Familial and sporadic 15q13.3 microdeletions in idiopathic generalized epilepsy: precedent for disorders with complex inheritance

Leanne M. Dibbens[1,2,*], Saul Mullen[4], Ingo Helbig[5,9], Heather C. Mefford[6,7], Marta A. Bayly[1], Susannah Bellows[4], Costin Leu[8,9], Holger Trucks[8,9], Tanja Obermeier[5,9], Michael Wittig[5,9], Andre Franke[5,9], Hande Caglayan[9,10], Zuhal Yapici[9,11], EPICURE Consortium[9†], Thomas Sander[8,9], Evan E. Eichler[6,7], Ingrid E. Scheffer[4,12], John C. Mulley[1,3] and Samuel F. Berkovic[4]

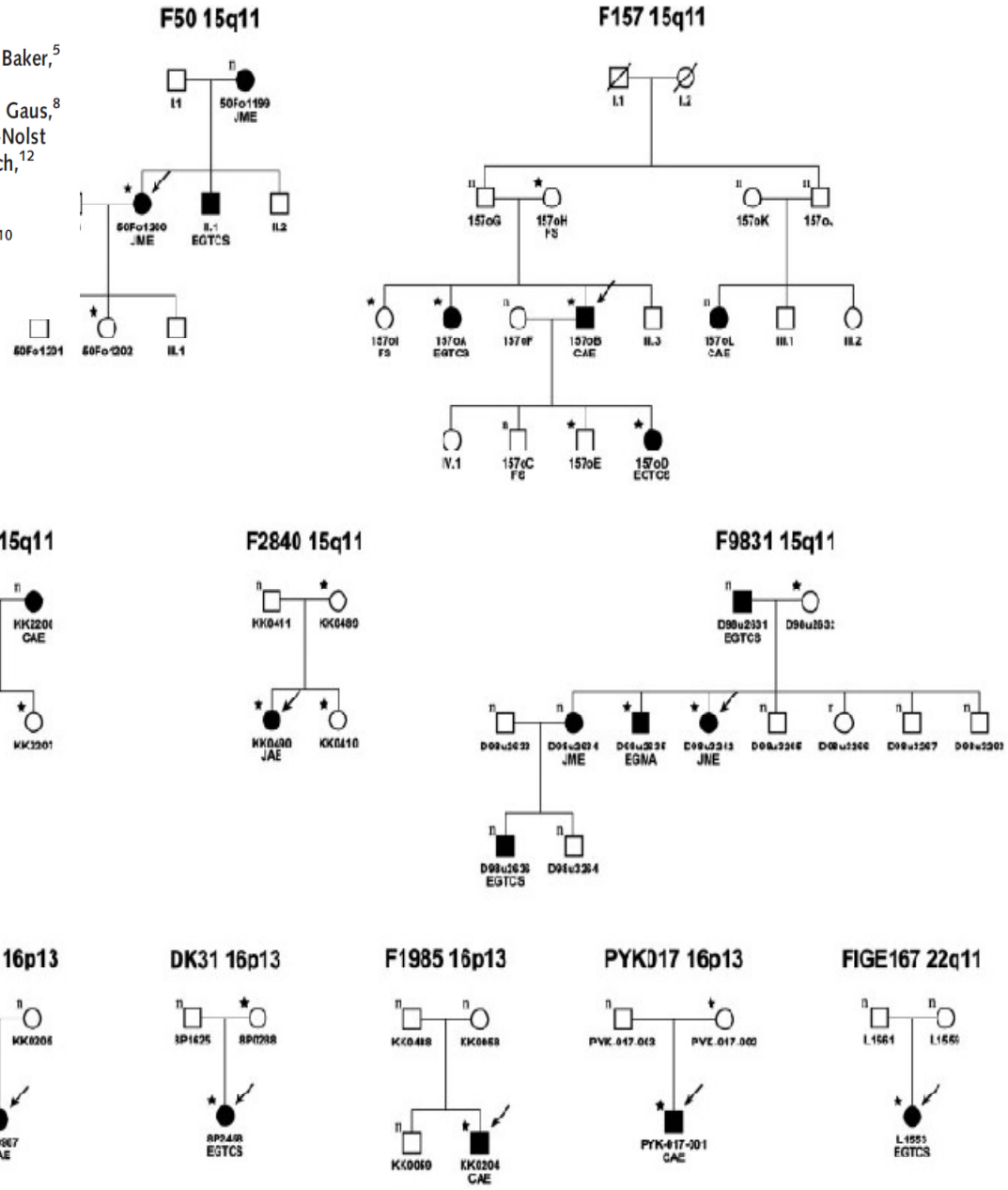
Human Molecular Genetics, 2009, Vol. 18, No. 19



Recurrent microdeletions at 15q11.2 and 16p13.11 predispose to idiopathic generalized epilepsies

Carolien G. F. de Kovel,[1,*] Holger Trucks,[2,*] Ingo Helbig,[3,*] Heather C. Mefford,[4,5] Carl Baker,[5] Costin Leu,[2] Christian Kluck,[2] Hiltrud Muhle,[3] Sarah von Spiczak,[3] Philipp Ostertag,[3] Tanja Obermeier,[3] Ailing A. Kleefuß-Lie,[6] Kerstin Hallmann,[6] Michael Steffens,[7] Verena Gaus,[8] Karl M. Klein,[9] Hajo M. Hamer,[9] Felix Rosenow,[9] Eva H. Brilstra,[1] Dorothée Kasteleijn-Nolst Trenité,[1] Marielle E. M. Swinkels,[1] Yvonne G. Weber,[10] Iris Unterberger,[11] Fritz Zimprich,[12] Lydia Urak,[13] Martha Feucht,[13] Karoline Fuchs,[14] Rikke S. Møller,[15,16] Helle Hjalgrim,[15] Peter De Jonghe,[17] Arvid Suls,[17] Ina-Maria Rückert,[18] Heinz-Erich Wichmann,[18,19,20] Andre Franke,[21] Stefan Schreiber,[21] Peter Nürnberg,[2] Christian E. Elger,[6] Holger Lerche,[10] Ulrich Stephani,[3] Bobby P. C. Koeleman,[1] Dick Lindhout,[1,22] Evan E. Eichler[5,23] and Thomas Sander[2,8]

Brain 2010: 133; 23–32 | 23



Genome-Wide Copy Number Variation in Epilepsy: Novel Susceptibility Loci in Idiopathic Generalized and Focal Epilepsies

Heather C. Mefford[1,2]*, Hiltrud Muhle[3], Philipp Ostertag[3], Sarah von Spiczak[3], Karen Buysse[4], Carl Baker[2], Andre Franke[5], Alain Malafosse[6], Pierre Genton[7], Pierre Thomas[8], Christina A. Gurnett[9], Stefan Schreiber[5], Alexander G. Bassuk[10], Michel Guipponi[6], Ulrich Stephani[3], Ingo Helbig[3], Evan E. Eichler[2,11]

Table 1. Phenotypes of probands evaluated by array CGH.

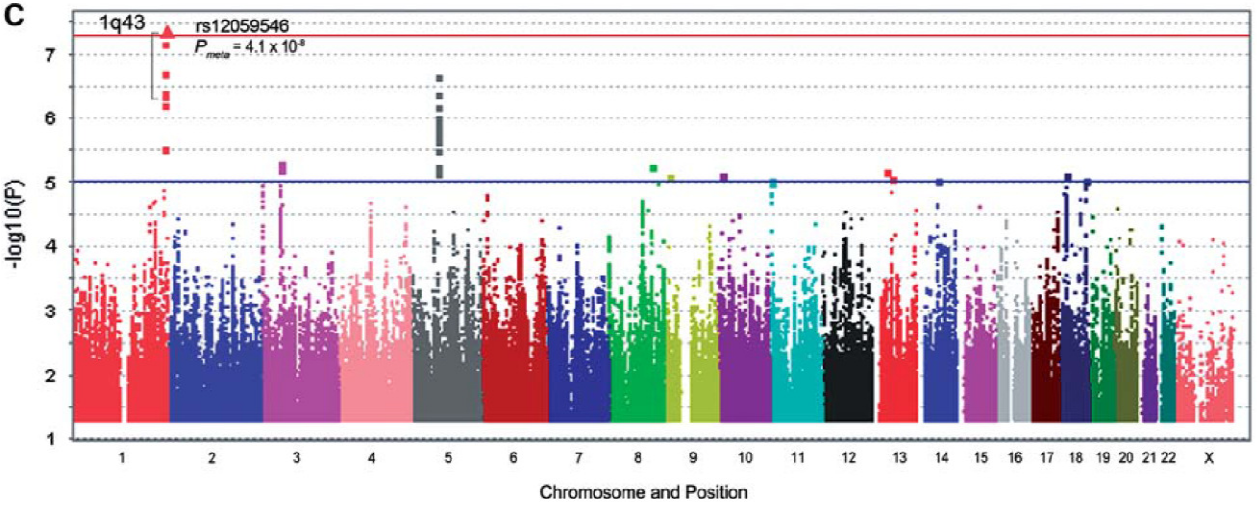
Type of epilepsy	N	Hotspot CNVs detected	Other CNVs detected	Total
IGE (n = 399)				
Juvenile myoclonic epilepsy (JME)	189	8^	9^	17
Absence epilepsy (AE)	94	5	5*	10
IGE with GTCS only	33	0	2	2
IGE unclassified	63	2	4	6
Benign myoclonic epilepsy of infancy	5	0	0	0
Myoclonic astatic epilepsy (MAE)	15	0	2	2
Idiopathic focal epilepsy (n = 63)				
BECTS	50	3	2	5
ABPE	13	0	0	0
Other (n = 55)				
ESES	4	0	0	0
Landau-Kleffner syndrome	3	0	0	0
Severe IGE of infancy (SIGEI)	15	1	1	2
West syndrome	4	0	2*	2
IC/NC	10	1	2*	3
Unclassified	19	0	2	2
Total	**517**	**20**	**31**	**51**

IGE, idiopathic generalized epilepsy; GTCS, generalized tonic-clonic seizures; BECTS, benign epilepsy with centrotemporal spikes; ABPE, atypical benign partial epilepsy; ESES, electrical status epilepticus during slow-wave sleep; IC, infantile convulsions; NC, neonatal convulsions;
*indicates two events in a single individual;
^two individuals (EMJ071 and EMJ117) each carrying one hotspot and one non-hotspot event.
doi:10.1371/journal.pgen.1000962.t001

Human Molecular Genetics, 2012, Vol. 21, No. 24 *5359–5372*
doi:10.1093/hmg/dds373
Advance Access published on September 4, 2012

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

EPICURE Consortium[†], EMINet Consortium[†], Michael Steffens[1], Costin Leu[2], Ann-Kathrin Ruppert[2], Federico Zara[3], Pasquale Striano[3], Angela Robbiano[3], Giuseppe Capovilla[4], Paolo Tinuper[5], Antonio Gambardella[6], Amedeo Bianchi[7], Angela La Neve[8], Giovanni Crichiutti[9], Carolien G.F. de Kovel[10], Dorothée Kasteleijn-Nolst Trenité[10], Gerrit-Jan de Haan[11], Dick Lindhout[10,11], Verena Gaus[12], Bettina Schmitz[12], Dieter Janz[12], Yvonne G. Weber[13], Felicitas Becker[13], Holger Lerche[13], Bernhard J. Steinhoff[14], Ailing A. Kleefuß-Lie[15], Wolfram S. Kunz[15], Rainer Surges[15], Christian E. Elger[15], Hiltrud Muhle[16], Sarah von Spiczak[16], Philipp Ostertag[16], Ingo Helbig[16], Ulrich Stephani[16], Rikke S. Møller[18,19], Helle Hjalgrim[18,20], Leanne M. Dibbens[21], Susannah Bellows[22], Karen Oliver[22], Saul Mullen[22], Ingrid E. Scheffer[22], Samuel F. Berkovic[22], Kate V. Everett[23], Mark R. Gardiner[24], Carla Marini[25], Renzo Guerrini[25], Anna-Elina Lehesjoki[26], Auli Siren[26,27], Michel Guipponi[28], Alain Malafosse[28], Pierre Thomas[29], Rima Nabbout[30], Stephanie Baulac[31], Eric Leguern[31], Rosa Guerrero[32,33], Jose M. Serratosa[32,33], Philipp S. Reif[34], Felix Rosenow[34], Martina Mörzinger[35], Martha Feucht[35], Fritz Zimprich[36], Claudia Kapser[37], Christoph J. Schankin[37], Arvid Suls[38,39], Katrin Smets[38,39,40], Peter De Jonghe[38,39], Albena Jordanova[41,42], Hande Caglayan[43], Zuhal Yapici[44], Destina A. Yalcin[47], Betul Baykan[45,46], Nerses Bebek[45,46], Ugur Ozbek[46], Christian Gieger[48], Heinz-Erich Wichmann[48,49,50], Tobias Balschun[17], David Ellinghaus[17], Andre Franke[17], Christian Meesters[1,51,‡], Tim Becker[1,51], Thomas F. Wienker[1], Anne Hempelmann[12,52], Herbert Schulz[52], Franz Rüschendorf[52], Markus Leber[1,2,51], Steffen M. Pauck[2], Holger Trucks[2], Mohammad R. Toliat[2], Peter Nürnberg[2], Giuliano Avanzini[53], Bobby P.C. Koeleman[10] and Thomas Sander[2,12,52,*]



Idiopathic Generalized Epilepsy (All)

Idiopathic Absence Epilepsy

Juvenile Myoclonic Epilepsy

doi:10.1093/brain/awq130 Brain 2010: 133; 2136–2147 | 2136

BRAIN
A JOURNAL OF NEUROLOGY

Common genetic variation and susceptibility to partial epilepsies: a genome-wide association study

Dalia Kasperavičiūtė,[1,*] Claudia B. Catarino,[1,2,*] Erin L. Heinzen,[3] Chantal Depondt,[4] Gianpiero L. Cavalleri,[5] Luis O. Caboclo,[1] Sarah K. Tate,[1] Jenny Jamnadas-Khoda,[1] Krishna Chinthapalli,[1] Lisa M. S. Clayton,[1] Kevin V. Shianna,[3] Rodney A. Radtke,[6] Mohamad A. Mikati,[7] William B. Gallentine,[7] Aatif M. Husain,[6] Saud Alhusaini,[5] David Leppert,[8,9] Lefkos T. Middleton,[8,10] Rachel A. Gibson,[8] Michael R. Johnson,[10] Paul M. Matthews,[8,10] David Hosford,[8] Kjell Heuser,[11] Leslie Amos,[8] Marcos Ortega,[12] Dominik Zumsteg,[12] Heinz-Gregor Wieser,[12] Bernhard J. Steinhoff,[13] Günter Krämer,[14] Jörg Hansen,[14] Thomas Dorn,[14] Anne-Mari Kantanen,[15] Leif Gjerstad,[11,16] Terhi Peuralinna,[17] Dena G. Hernandez,[18] Kai J. Eriksson,[19] Reetta K. Kälviäinen,[15,20] Colin P. Doherty,[21] Nicholas W. Wood,[22] Massimo Pandolfo,[4] John S. Duncan,[1,2] Josemir W. Sander,[1,2,23] Norman Delanty,[5] David B. Goldstein[3] and Sanjay M. Sisodiya[1,2]

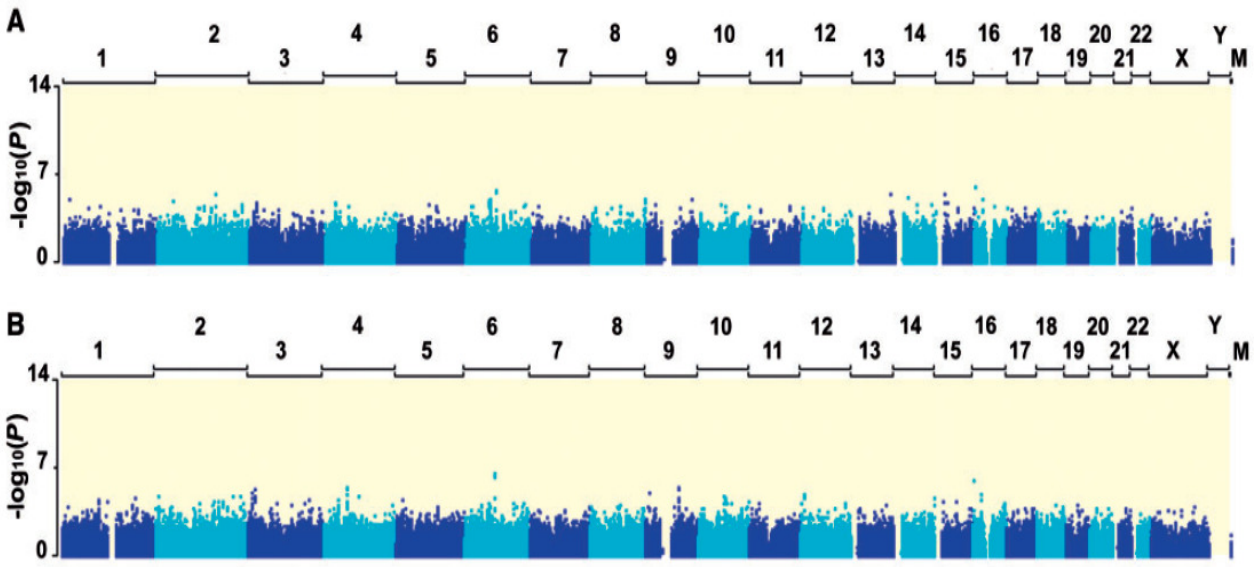
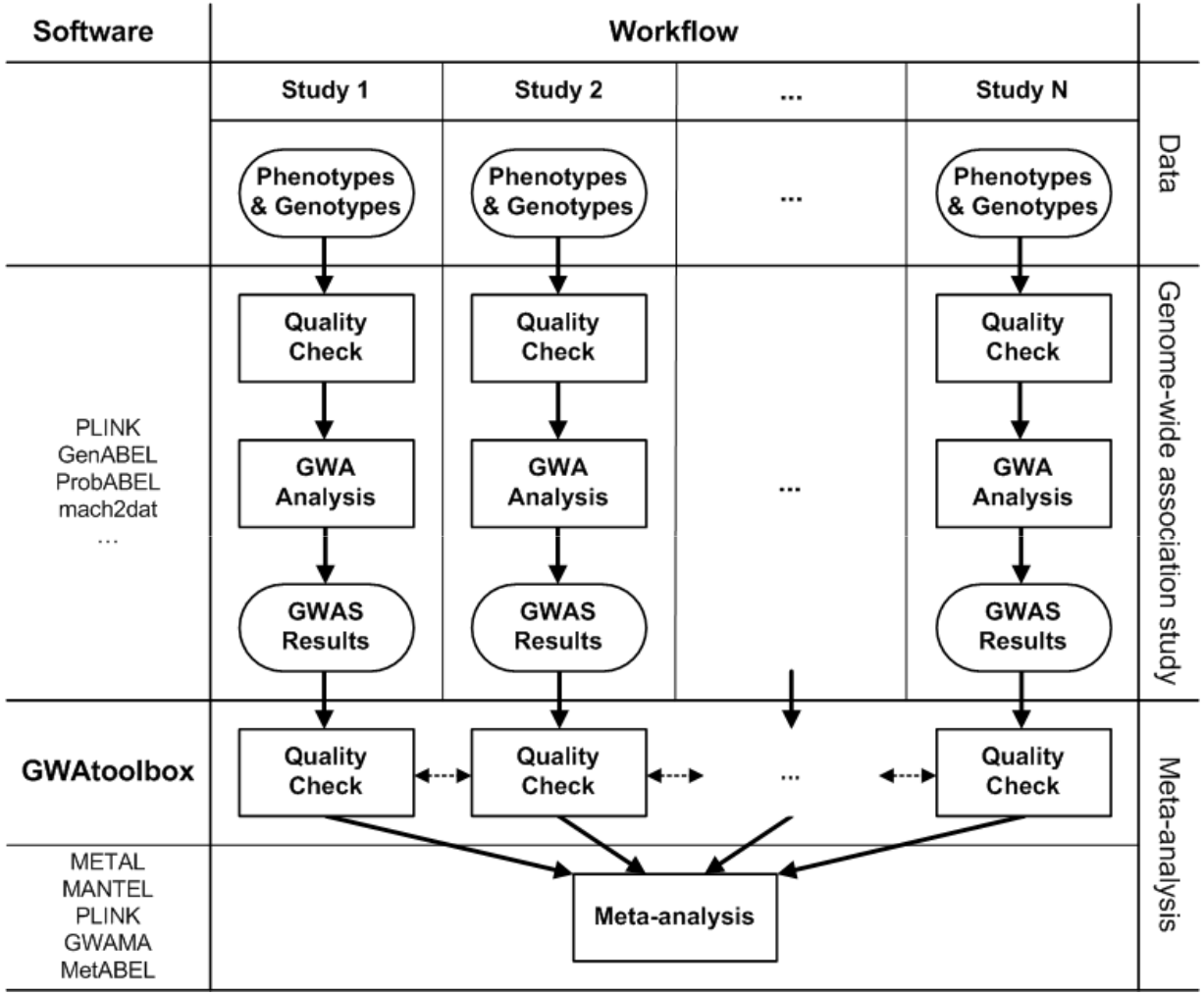


Figure 3 Manhattan plots for genome-wide association-analysis results. $-\log_{10}$ *P*-values of the logistic regression test (**A**) and the Cochran–Mantel–Haenszel test (**B**) for quality-control-positive SNPs are plotted against SNP positions on each chromosome. Chromosomes are shown in alternating colours for clarity.


Software
Workflow
Study 1
Study 2
...
Study N
Data
Phenotypes & Genotypes
Phenotypes & Genotypes
...
Phenotypes & Genotypes
Genome-wide association study
PLINK
GenABEL
ProbABEL
mach2dat
...
Quality Check
GWA Analysis
GWAS Results
Quality Check
GWA Analysis
GWAS Results
...
Quality Check
GWA Analysis
GWAS Results
Meta-analysis
GWAtoolbox
Quality Check
Quality Check
...
Quality Check
METAL
MANTEL
PLINK
GWAMA
MetABEL
Meta-analysis

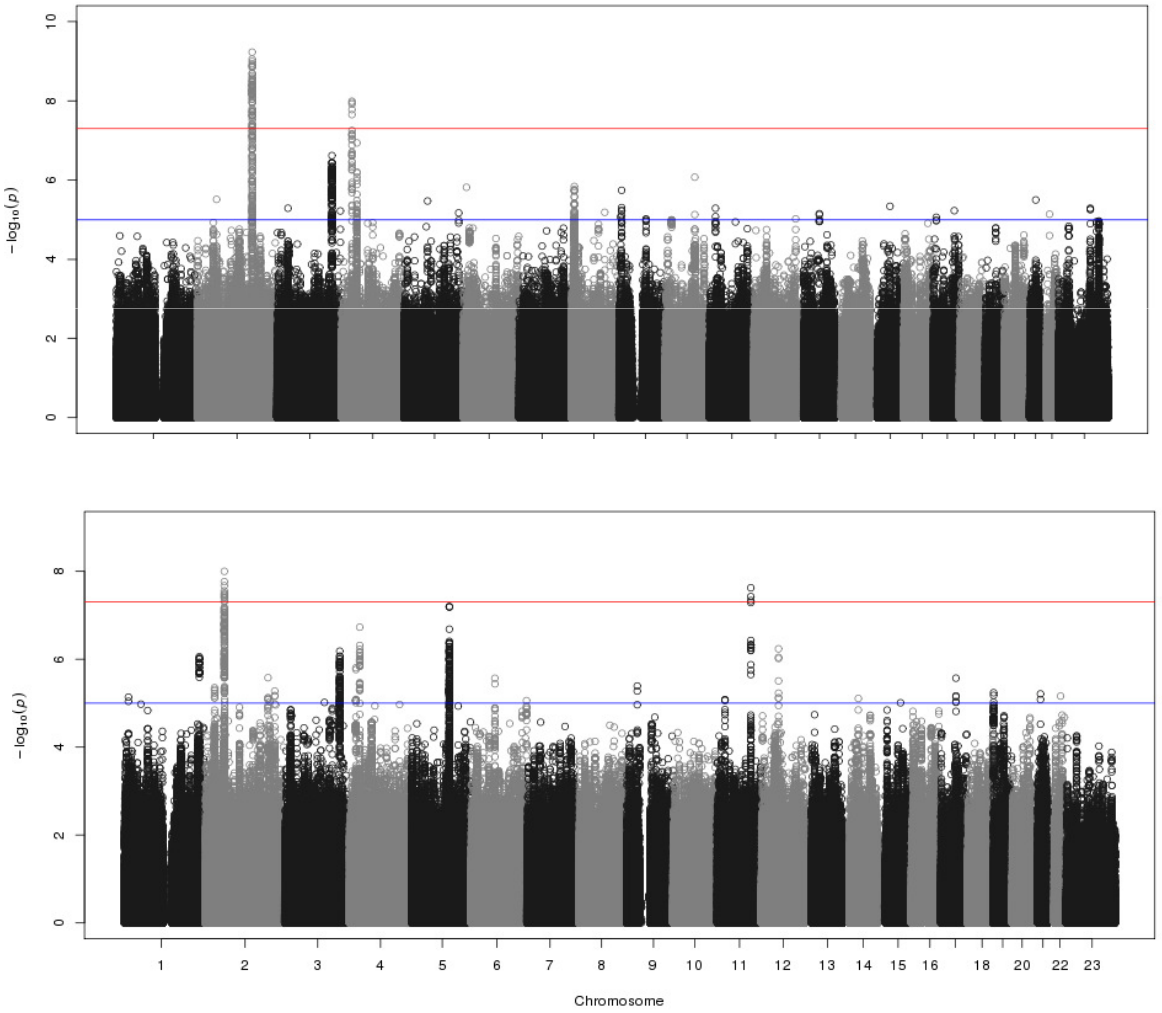
International League Against Epilepsy
International Consortium
on the Genetics of Epilepsies

London, Royal Society, 26th March 2012

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

*International League Against Epilepsy Consortium on Complex Epilepsies**

Lancet Neurol 2014;
13: 893–903



9,681 Epilepsy cases
vs
25,824 controls

2,607 IGE cases
vs
18,987 controls

Common Disease – Rare Variants Hypothesis

Evolution and Functional Impact of Rare Coding Variation from Deep Sequencing of Human Exomes

Jacob A. Tennessen,[1*] Abigail W. Bigham,[2*†] Timothy D. O'Connor,[1*] Wenqing Fu,[1] Eimear E. Kenny,[3] Simon Gravel,[3] Sean McGee,[1] Ron Do,[4,5] Xiaoming Liu,[6] Goo Jun,[7] Hyun Min Kang,[7] Daniel Jordan,[8] Suzanne M. Leal,[9] Stacey Gabriel,[4] Mark J. Rieder,[1] Goncalo Abecasis,[7] David Altshuler,[4] Deborah A. Nickerson,[1] Eric Boerwinkle,[6,10] Shamil Sunyaev,[4,8] Carlos D. Bustamante,[3] Michael J. Bamshad,[1,2‡] Joshua M. Akey,[1‡] Broad GO, Seattle GO, on behalf of the NHLBI Exome Sequencing Project

Exome Sequencing of 2440 individuals (1351 European, 1088 African)

Population data

- 500.000 different coding SNPs
- 86% rare (< 0,5%)
- 82% previously unknown
- 82% population specific

Individual data

- ~13.595 coding SNPs
- ~ 320 functional coding SNPs
- 97,5% of functional important SNPs rare

6 JULY 2012 VOL 337 SCIENCE

Exome Sequencing of Ion Channel Genes Reveals Complex Profiles Confounding Personal Risk Assessment in Epilepsy

Tara Klassen,[1] Caleb Davis,[1] Alica Goldman,[1] Dan Burgess,[1] Tim Chen,[1] David Wheeler,[4] John McPherson,[3,4] Traci Bourquin,[4] Lora Lewis,[4] Donna Villasana,[4] Margaret Morgan,[4] Donna Muzny,[4] Richard Gibbs,[3,4] and Jeffrey Noebels[1,2,3,*]

[1]Department of Neurology
[2]Department of Neuroscience
[3]Department of Molecular and Human Genetics
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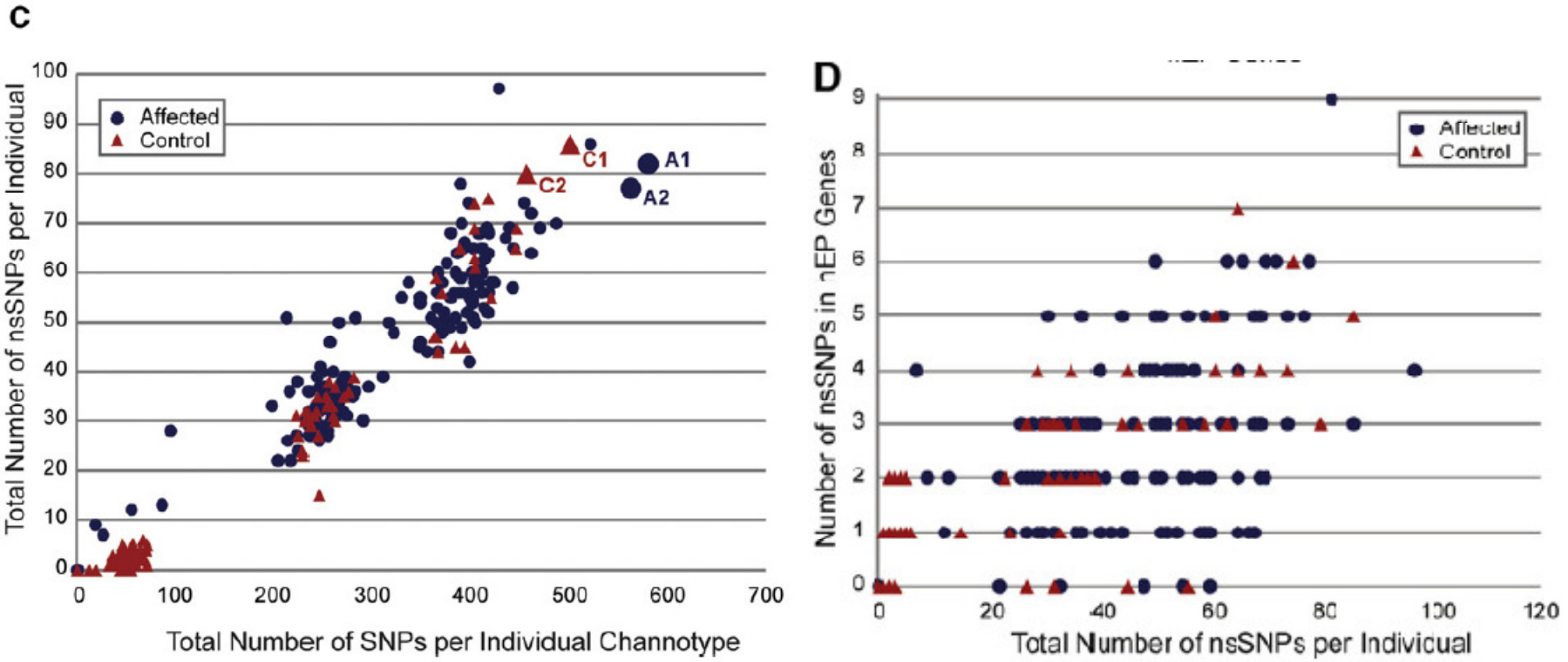
Baylor College of Medicine, Houston, TX 77030, USA
*Correspondence: jnoebels@bcm.edu
DOI 10.1016/j.cell.2011.05.025



The promise of genomics

1989

2003

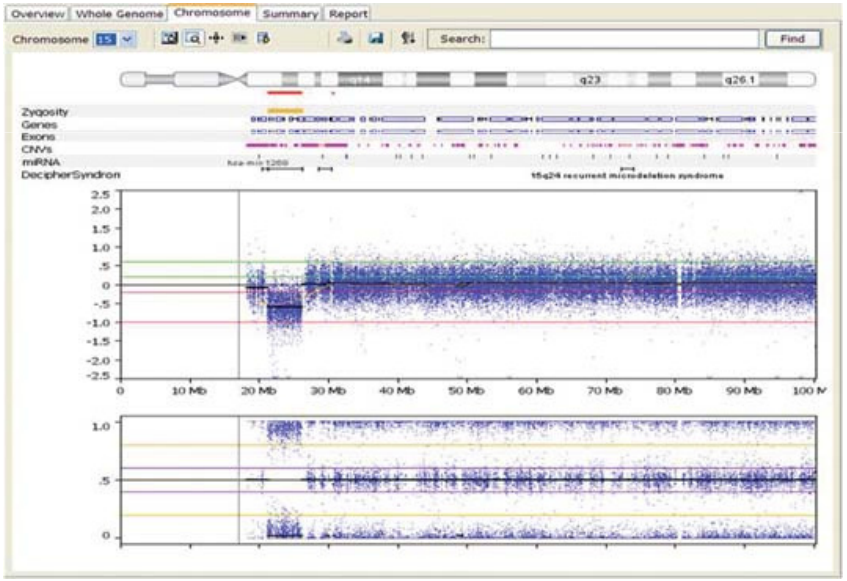
2010

2012

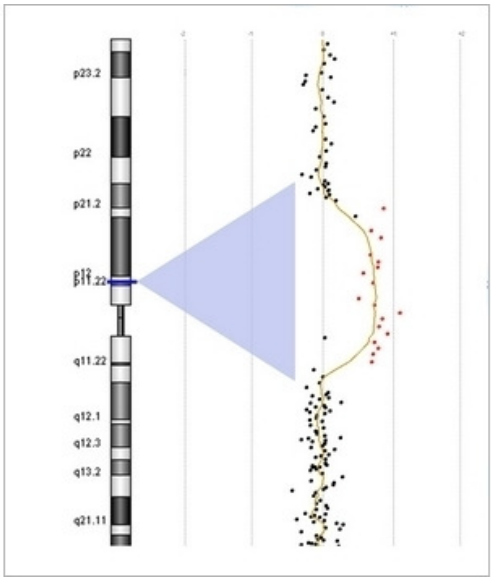
DIRECT IDENTIFICATION OF MUTATIONS: GENOME-WIDE APPROACHES

Copy Number Variations (CNVs)

SNP Arrays



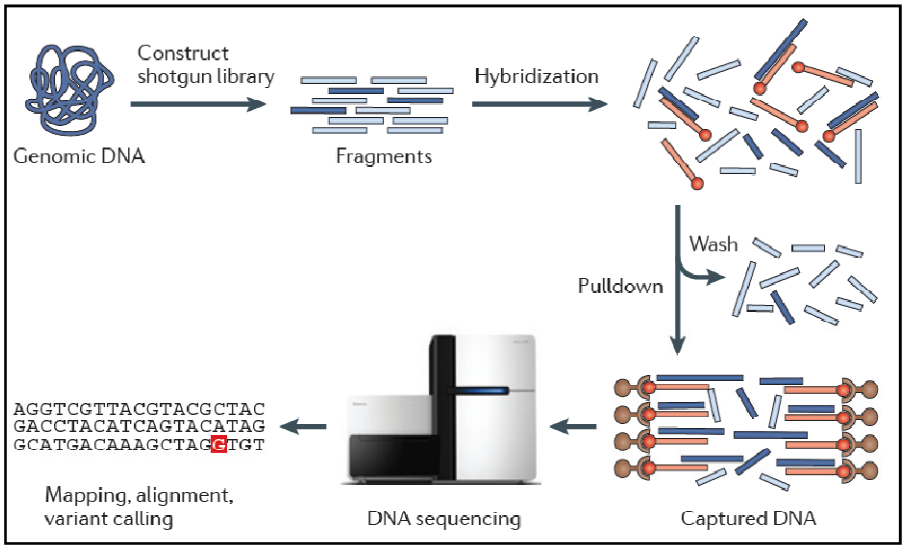
CGH-Arrays

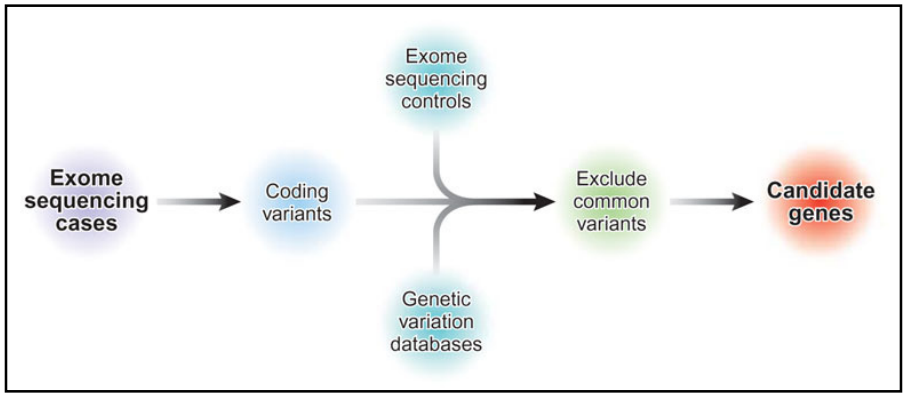


DIRECT IDENTIFICATION OF MUTATIONS: GENOME-WIDE APPROACHES

Next-Generation Sequencing (Point and Indel mutations)

Exome Sequencing





Epilepsia, 54(2), 265–271, 2013
doi: 10.1111/epi.12084

FULL-LENGTH ORIGINAL RESEARCH

Rare exonic deletions of the *RBFOX1* gene increase risk of idiopathic generalized epilepsy

*†‡[1,2]Dennis Lal, *[1,2]Holger Trucks, §[1,2]Rikke S. Møller, §[1,2]Helle Hjalgrim, ¶[2]Bobby P. C. Koeleman, ¶[2]Carolien G. F.de Kovel, #Frank Visscher, **[1,2]Yvonne G. Weber, **[1,2]Holger Lerche, **[1,2]Felicitas Becker, ††Christoph J. Schankin, †Bernd A. Neubauer, ‡‡[1,2]Rainer Surges, ‡‡[1,2]Wolfram S. Kunz, §§[2]Fritz Zimprich, ¶¶Andre Franke, ##Thomas Illig, ***Janina S. Ried, *[1,2]Costin Leu, *[1,2]Peter Nürnberg, *[1,2]Thomas Sander, [1]EMINet Consortium, and [2]EPICURE Consortium

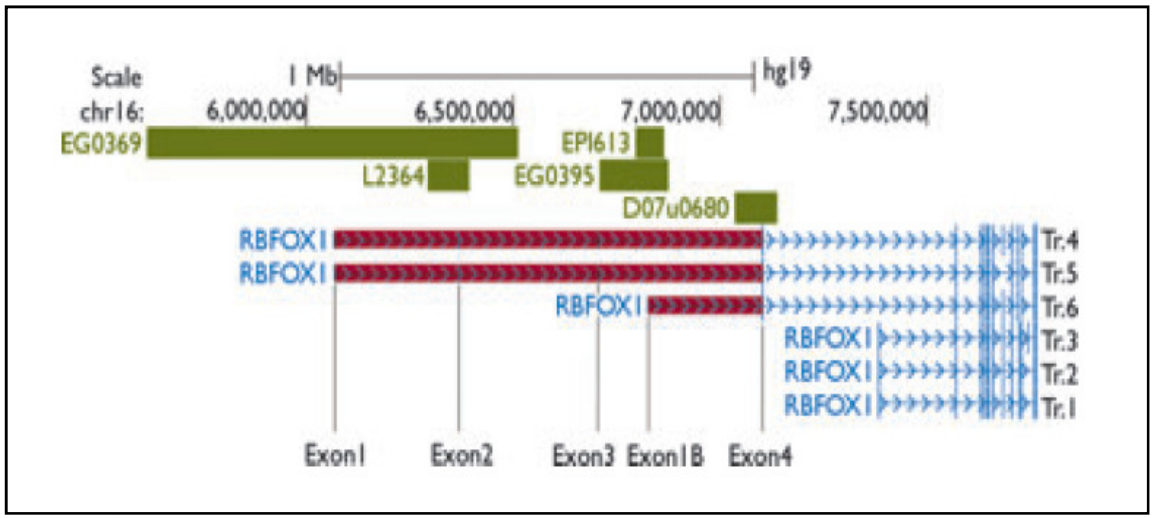
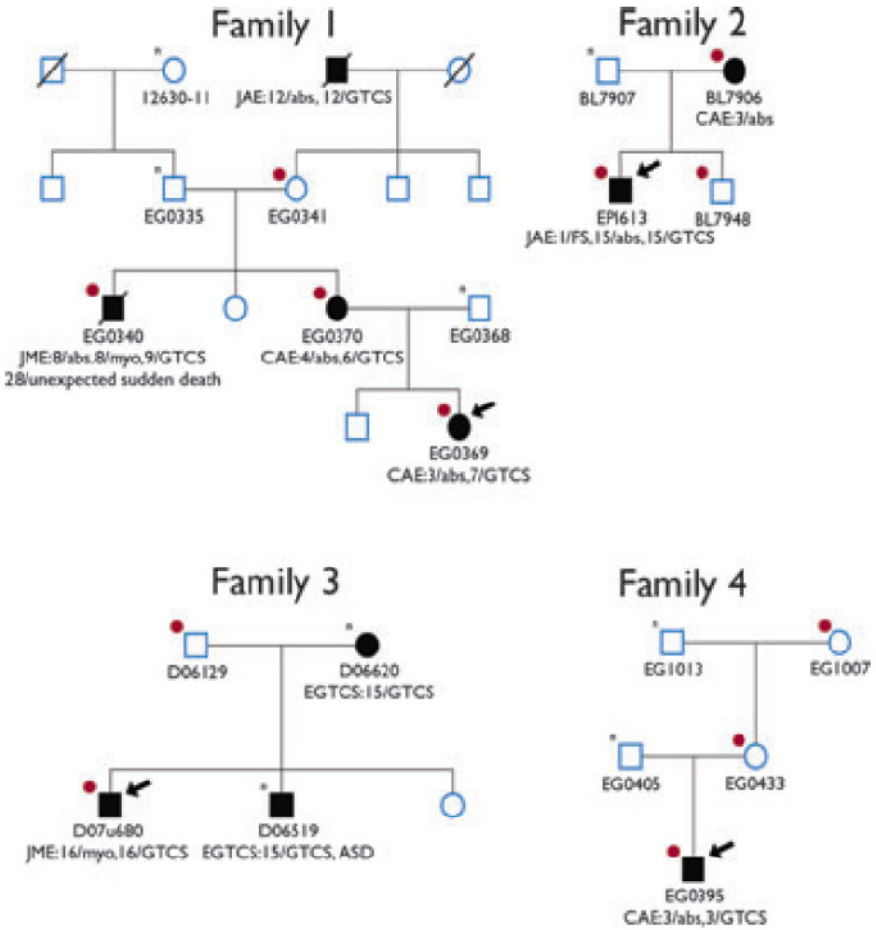


Table 1. *RBFOX1* exon-disrupting deletions in IGE index patients

Family	Index patient	Deletion size (kb)	Breakpoints at chr16 (Mb)	Diagnosis/age-at-onset/seizure types	Familial comorbidity
1	EG0369	896	5.616–6.512	CAE:3/abs,7/GTCS	Developmental delay, LD, sudden death
2	EPI613	68	6.797–6.865	JAE:1/FS,15/abs,15/GTCS	No neuropsychiatric disorders
3	D07u0680	103	7.035–7.138	JME:16/myo,16/GTCS	ASD, LD, myopia
4	EG0395	165	6.709–6.874	CAE:3/abs, 3/GTCS	No neuropsychiatric disorders
–	L2364	100	6.294–6.394	JME:14/myo,14/GTCS	No neuropsychiatric disorders

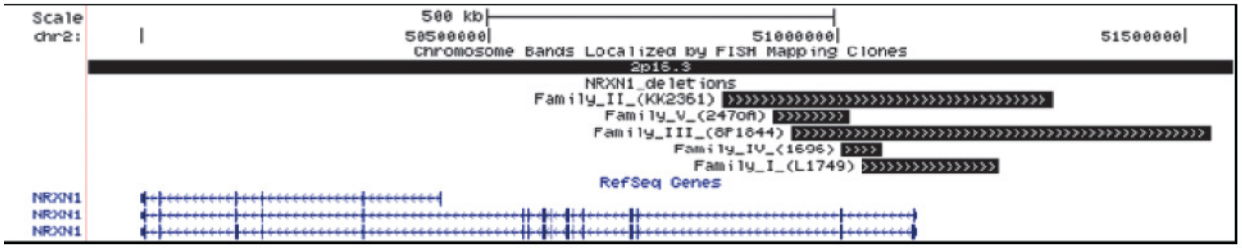


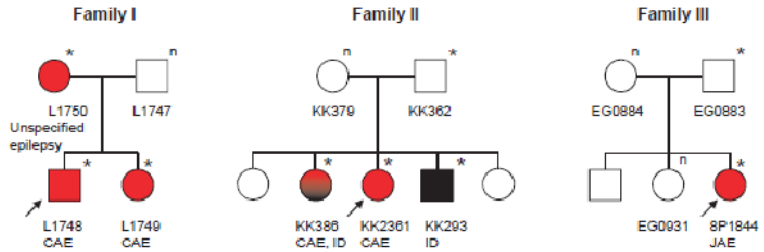
Epilepsia, 54(2), 256–264, 2013
doi: 10.1111/epi.12078

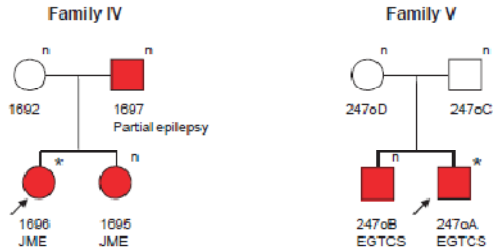
FULL-LENGTH ORIGINAL RESEARCH

Exon-disrupting deletions of *NRXN1* in idiopathic generalized epilepsy

[1,2]*Rikke S. Møller, [1,2]†Yvonne G. Weber, [1]*‡Laura L. Klitten, [2]§Holger Trucks, [2]¶Hiltrud Muhle, [2]#Wolfram S. Kunz, **Heather C. Mefford, ††Andre Franke, ‡‡Monika Kautza, *Peter Wolf, §§Dieter Dennig, ††Stefan Schreiber, ¶¶Ina-Maria Rückert, ¶¶,##,***H.-Erich Wichmann, †††,‡‡‡Jan P. Ernst, §§§Claudia Schurmann, ¶¶¶Hans J. Grabe, ‡Niels Tommerup, [2]¶Ulrich Stephani, [2]†Holger Lerche, [2]*###Helle Hjalgrim, [2]¶Ingo Helbig, [2]§Thomas Sander, and [2]EPICURE Consortium







CNVs in Ion Channels genes in IGE

- **440** genes encoding protiens involved in transmembrane transport of ions or neutransmitters
- **60.000** probes covering introns and exons of candidate genes (spacing range 100 – 1.000 bp)
- **44.000** genome-wide backbone probes (average spacing 75 kb)

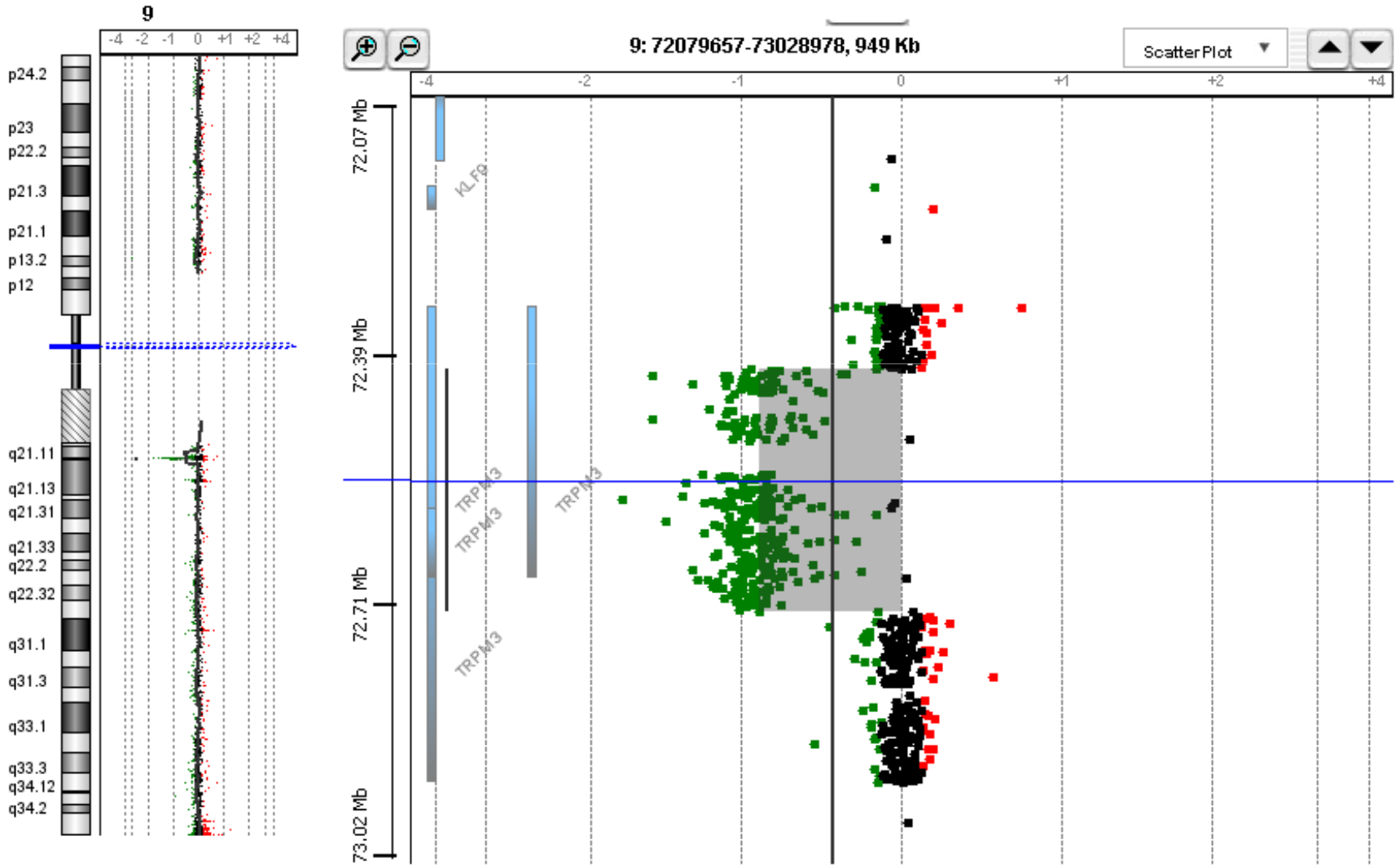
- **227** familial cases of IGE/GEFS+ (two affected cases)
- **248** controls

✓ Identification of **rare highly penetrant** CNVs

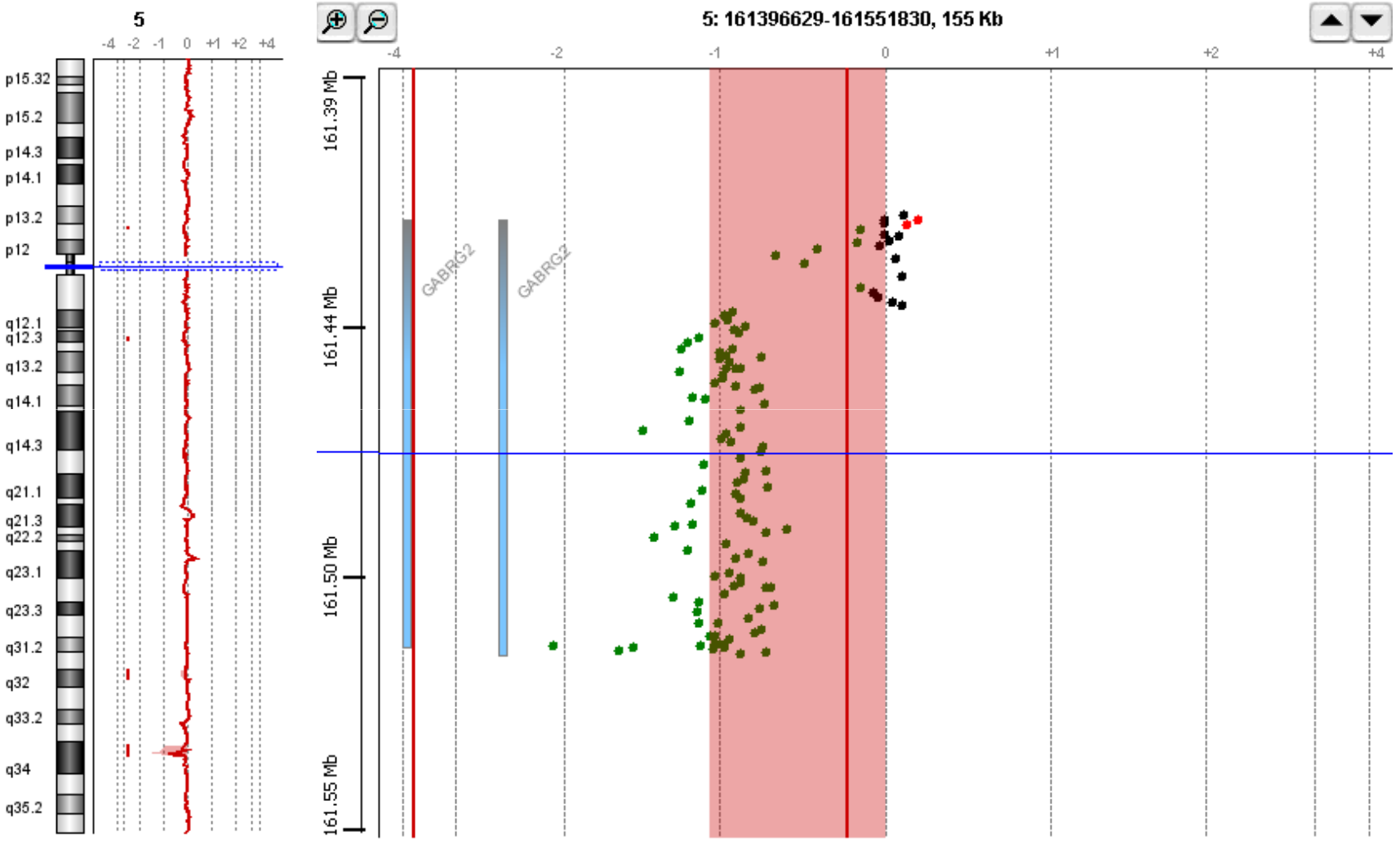
✓ Identification of **common recurrent** CNVs

✓ **Functional studies**

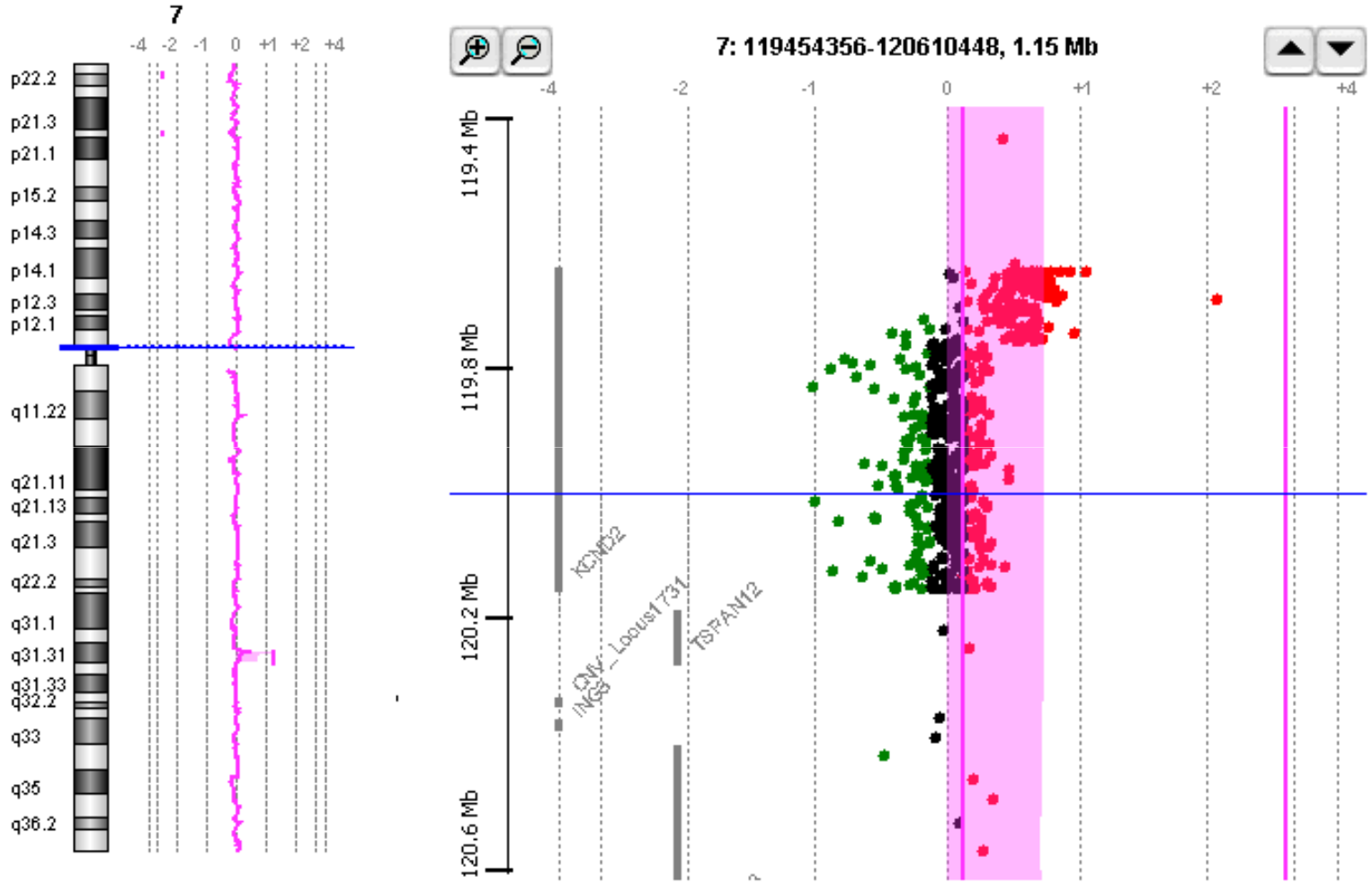
TRANSIENT RECEPTOR POTENTIAL CATION CHANNEL, SUBFAMILY M, MEMBER 3; TRPM3



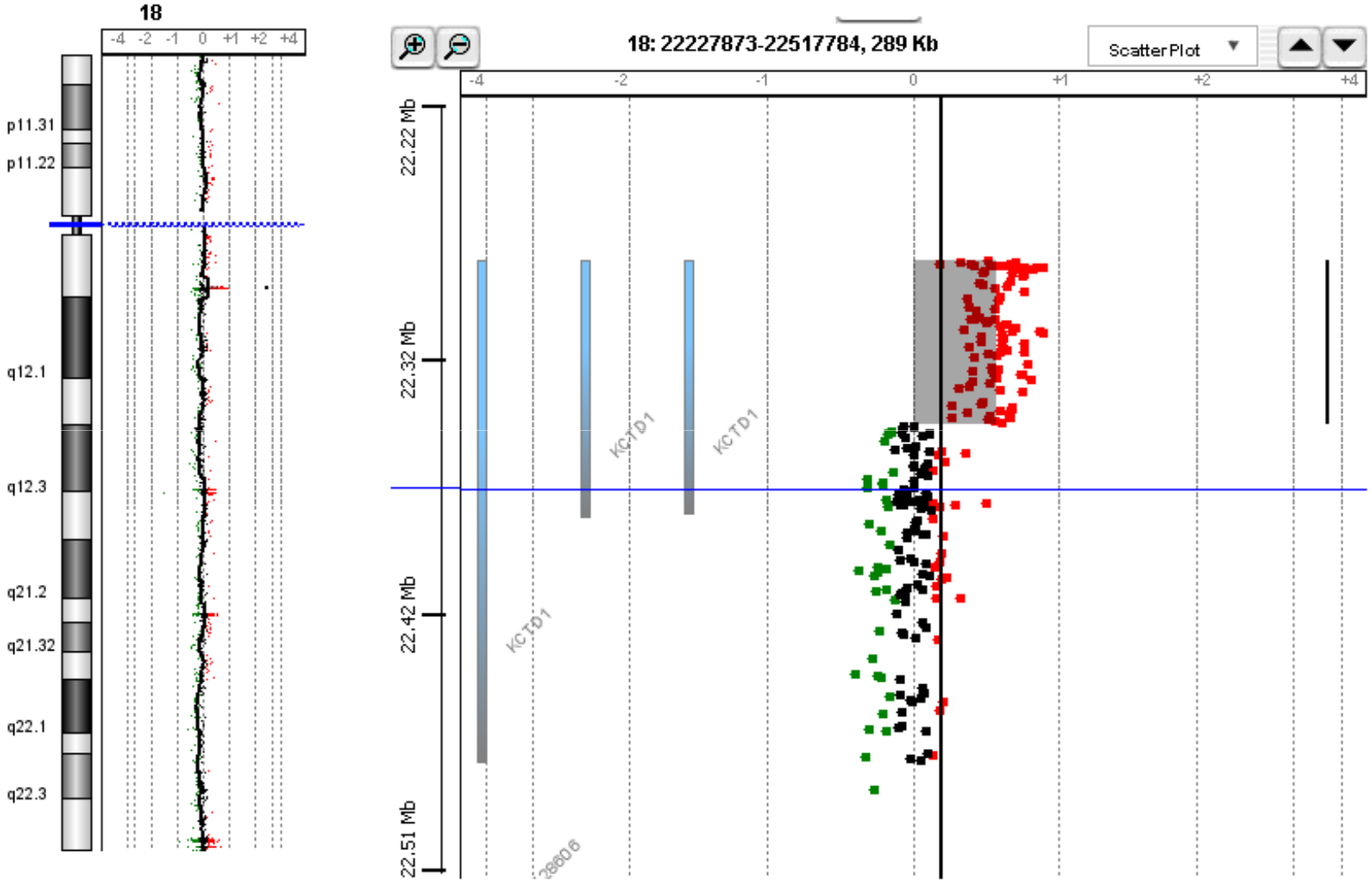
GAMMA-AMINOBUTYRIC ACID RECEPTOR, GAMMA-2; GABRG2

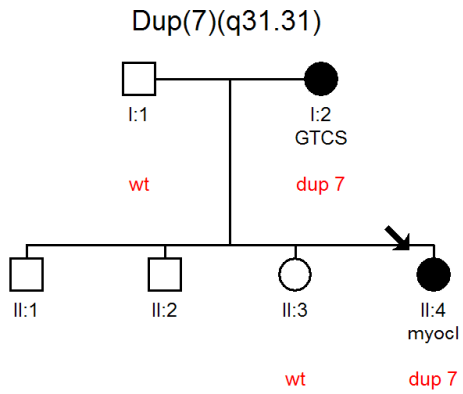


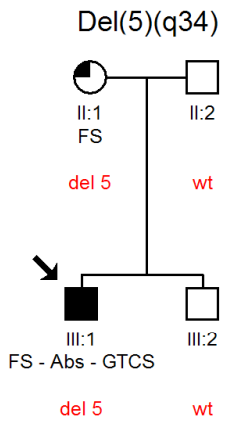
POTASSIUM VOLTAGE-GATED CHANNEL, SHAL-RELATED SUBFAMILY, MEMBER 2; KCND2

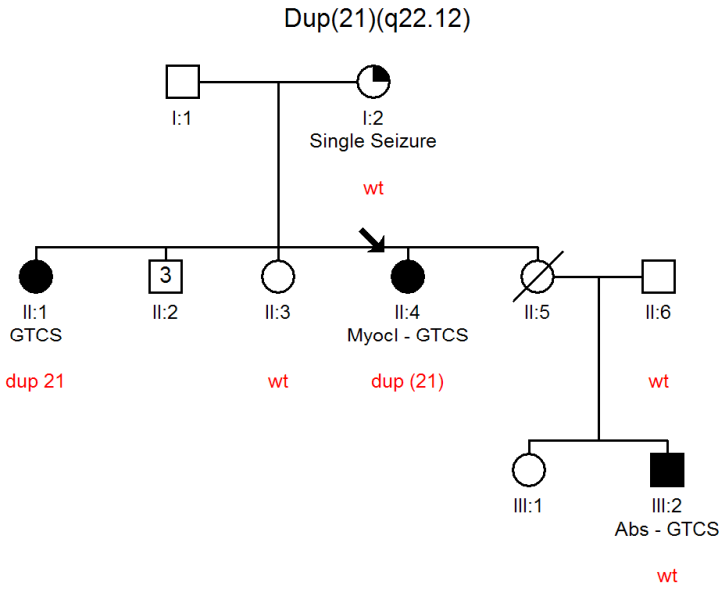


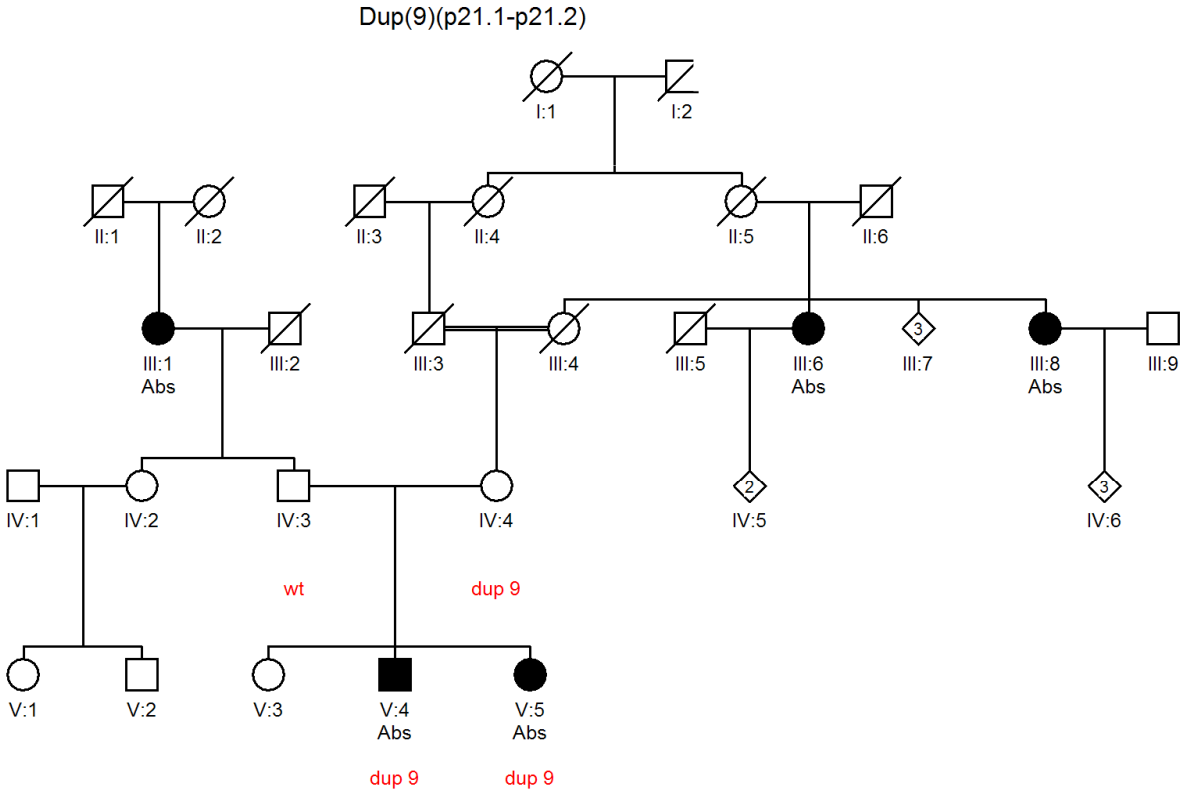
POTASSIUM CHANNEL TETRAMERIZATION DOMAIN-CONTAINING 1; KCTD1

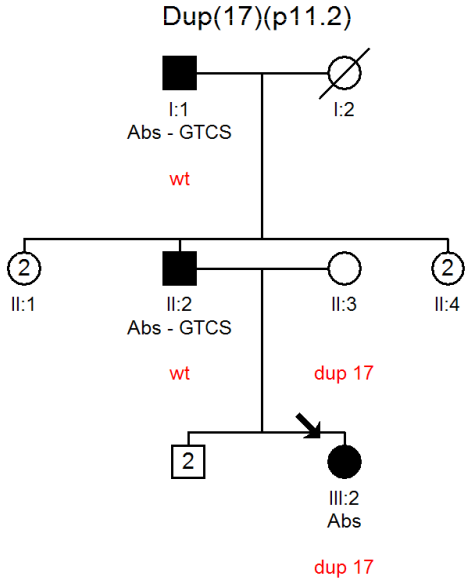



Dup(7)(q31.31)
I:1
I:2
GTCS
wt
dup 7
II:1
II:2
II:3
II:4
myocl
wt
dup 7


Del(5)(q34)
II:1
FS
II:2
del 5
wt
III:1
FS - Abs - GTCS
III:2
del 5
wt


Dup(21)(q22.12)
I:1
I:2
Single Seizure
wt
II:1
GTCS
3
II:2
II:3
II:4
Myocl - GTCS
II:5
II:6
dup 21
wt
dup (21)
wt
III:1
III:2
Abs - GTCS
wt


Dup(9)(p21.1-p21.2)
I:1
I:2
II:1
II:2
II:3
II:4
II:5
II:6
III:1
Abs
III:2
III:3
III:4
III:5
III:6
Abs
III:7
III:8
Abs
III:9
IV:1
IV:2
IV:3
IV:4
2
IV:5
3
IV:6
wt
dup 9
V:1
V:2
V:3
V:4
Abs
V:5
Abs
dup 9
dup 9

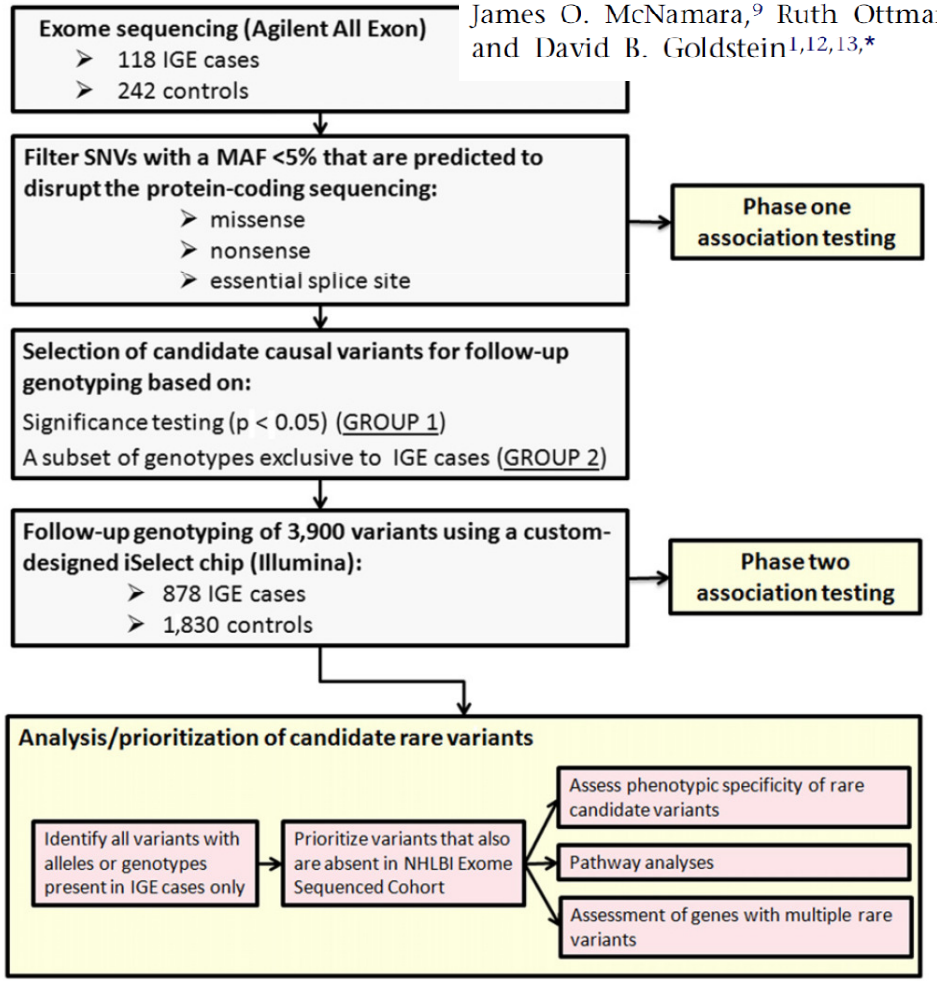

Dup(17)(p11.2)
I:1
Abs - GTCS
I:2
wt
2
II:1
II:2
Abs - GTCS
II:3
2
II:4
wt
dup 17
2
III:2
Abs
dup 17

The American Journal of Human Genetics 91, 293–302, August 10, 2012

ARTICLE

Exome Sequencing Followed by Large-Scale Genotyping Fails to Identify Single Rare Variants of Large Effect in Idiopathic Generalized Epilepsy

Erin L. Heinzen,[1,2,*] Chantal Depondt,[3] Gianpiero L. Cavalleri,[4] Elizabeth K. Ruzzo,[1] Nicole M. Walley,[1] Anna C. Need,[1,2] Dongliang Ge,[1,2] Min He,[1] Elizabeth T. Cirulli,[1] Qian Zhao,[1] Kenneth D. Cronin,[1] Curtis E. Gumbs,[1] C. Ryan Campbell,[1] Linda K. Hong,[1] Jessica M. Maia,[1] Kevin V. Shianna,[1,2] Mark McCormack,[4] Rodney A. Radtke,[5] Gerard D. O'Conner,[6] Mohamad A. Mikati,[7] William B. Gallentine,[7] Aatif M. Husain,[5] Saurabh R. Sinha,[5] Krishna Chinthapalli,[8] Ram S. Puranam,[9] James O. McNamara,[9] Ruth Ottman,[10,11] Sanjay M. Sisodiya,[8] Norman Delanty,[4,6,13] and David B. Goldstein[1,12,13,*]



epi4K
GENE DISCOVERY IN EPILEPSY

Epi4K - Gene Discovery in Epilepsy

Login

- Home Epi4K
- Mission
- Cores
- Projects
- Institutions
- Documents
- Press Releases
- Resources

Epi4K:

Our goal is to elucidate the genetic bases of the epilepsies with an ultimate goal to improve the care of patients with epilepsy.

Cores:

Administrative Core

Phenotyping and Clinical Informatics (PCI) Core

Sequencing, Biostatistics and Bioinformatics (SBB) Core

Projects

Project 1:
Epileptic Encephalopathies

Project 2:
Whole Genome Sequencing in Multiplex Families and Pairs

Project 3:
Prognosis (Status: Planned)

Project 4:
CNV Detection

European Science Foundation

EUROCORES Programme

EuroEPINOMICS

Functional Genomic Variation in the Epilepsies

HOME | ABOUT US | FOR PARTICIPANTS | CONTACT

You are here: Home ▸ Projects

- Home
- Social Media
- Publications
- Events
- Networking and Dissemination Activities
- Projects
  - RES
  - Epiglia
  - EpiGENet
  - CoGIE
- Governing Bodies
- Working plan for EuroEPINOMICS

Collaborative Research Projects (CRPs)

The following projects are funded under the EUROCORES programme EuroEPINOMICS:

CRP Acronym	CRP Title	Project Leader
RES	Genetics of rare epilepsy syndromes	Professor Peter de Jonghe
Epiglia	GENETIC TARGETS OF EPILEPTOGENESIS AND PHARMACORESISTANCE IN BRAIN GLIAL CELLS. A translational research project on the genetic and molecular pathways of Temporal Lobe Epilepsy and Febrile Seizures	Professor Erik Taubøll
EpiGENet	Epigenetic pathomechanisms promoting epileptogenesis in focal and generalized epilepsies	Professor Asla Pitkänen
CoGIE	Complex genetics of idiopathic epilepsies	Professor Holger Lerche

European Commission

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Health

European Commission > Research & Innovation > Health > Medical Research > Brain Research

- Home
- Projects
  - FP7 projects
  - FP6 projects
  - Search projects
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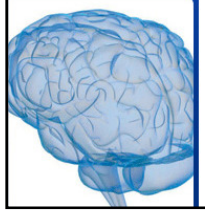
- Contact Corner
- e-library



DESIRE

Development and Epilepsy - Strategies for Innovative Research to improve diagnosis, prevention and treatment in children with difficult to treat Epilepsy

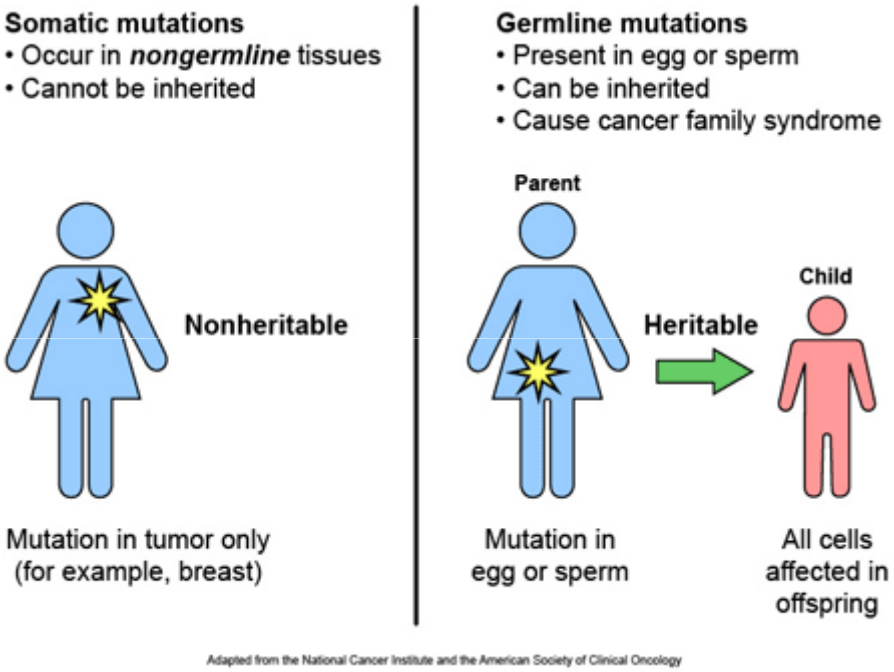
Coordinator: Renzo GUERRINI
Project Number: 602531
EC contribution: € 11,995,646.00
Project website: DESIRE

DESIRE will focus on epileptogenic developmental disorders EDD, i.e. early onset epilepsies whose origin is closely related to developmental brain processes. A major cause of EDD are malformations of cortical development (MCD), either macroscopic or subtle. EDD are often manifested as epileptic encephalopathies (EE), i.e. conditions in which epileptic activity itself may contribute to severe cognitive and behavioral impairments. EDD are the most frequent drug-resistant pediatric epilepsies carrying a lifelong perspective of disability and reduced quality of life.

Although EDD collectively represent a major medical and socio-economic burden, their molecular diagnosis, pathogenic mechanisms (PM) and rationale treatment are poorly understood. Specific objectives of DESIRE are to advance the state of the art with respect to:

1. the genetic and epigenetic causes and PM of EDD, particularly epileptogenic MCD, to elucidate molecular networks and disrupted protein complexes and search for common bases for these apparently heterogeneous disorders.
2. the diagnostic tools (biomarkers) and protocols through the study of a unique and well-characterized cohort of children to provide standardized diagnosis for patient stratification and research across Europe.
3. treatment of EDD using randomized, multidisciplinary clinical protocols and testing preclinical strategies in experimental models to also address novel preventative strategies.

De novo mutations



1 de novo nonsynonymous coding SNP is expected to occur in each individual

A genomic view of mosaicism and human disease

Leslie G. Biesecker[1] and Nancy B. Spinner[2]

Abstract | Genomic technologies, including next-generation sequencing (NGS) and single-nucleotide polymorphism (SNP) microarrays, have provided unprecedented opportunities to
It has long been k
apparent in a div
distributions and
causative mosaic
insight into the p
clinical and mole
gained from thes

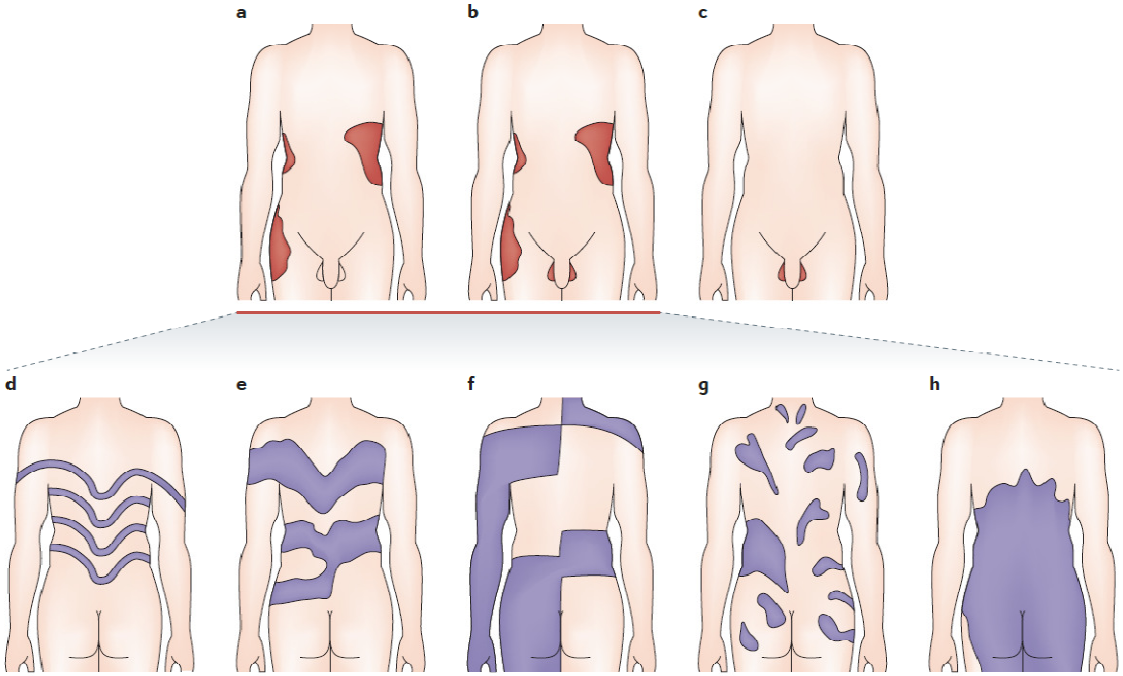
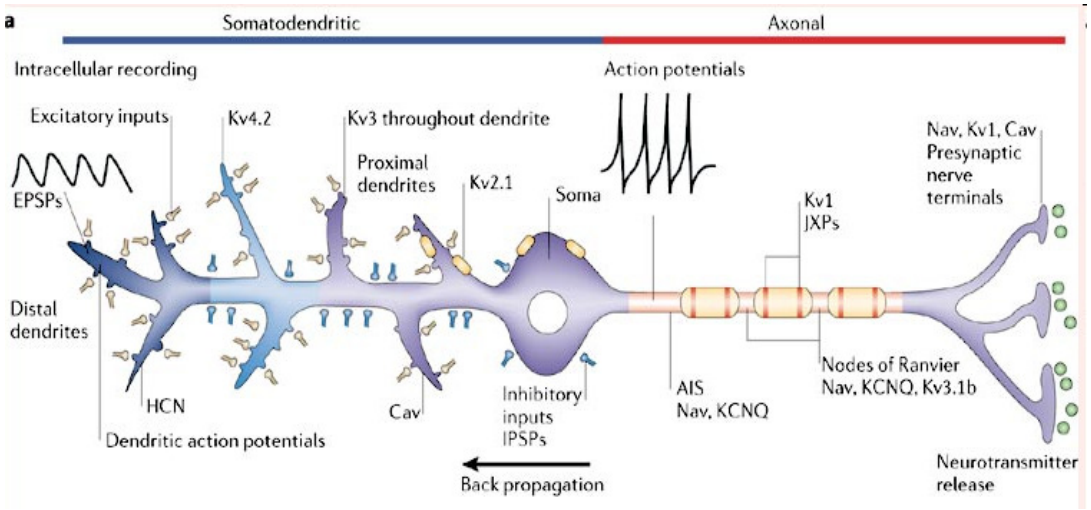
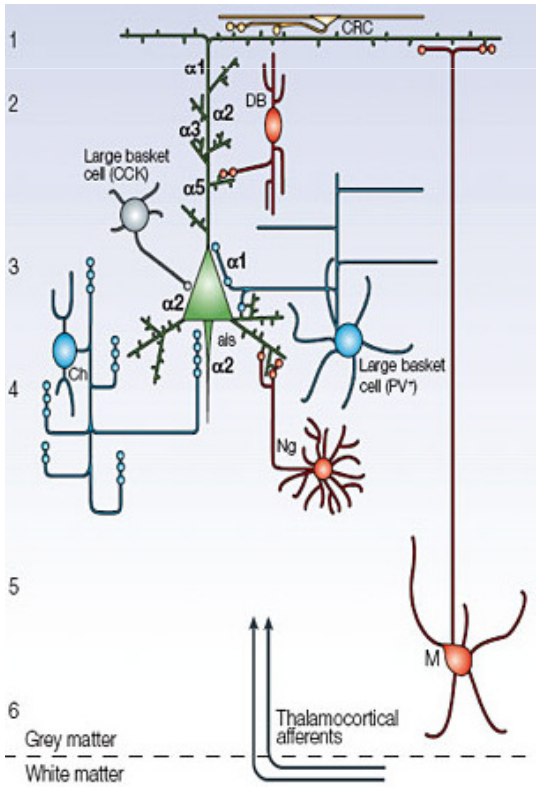
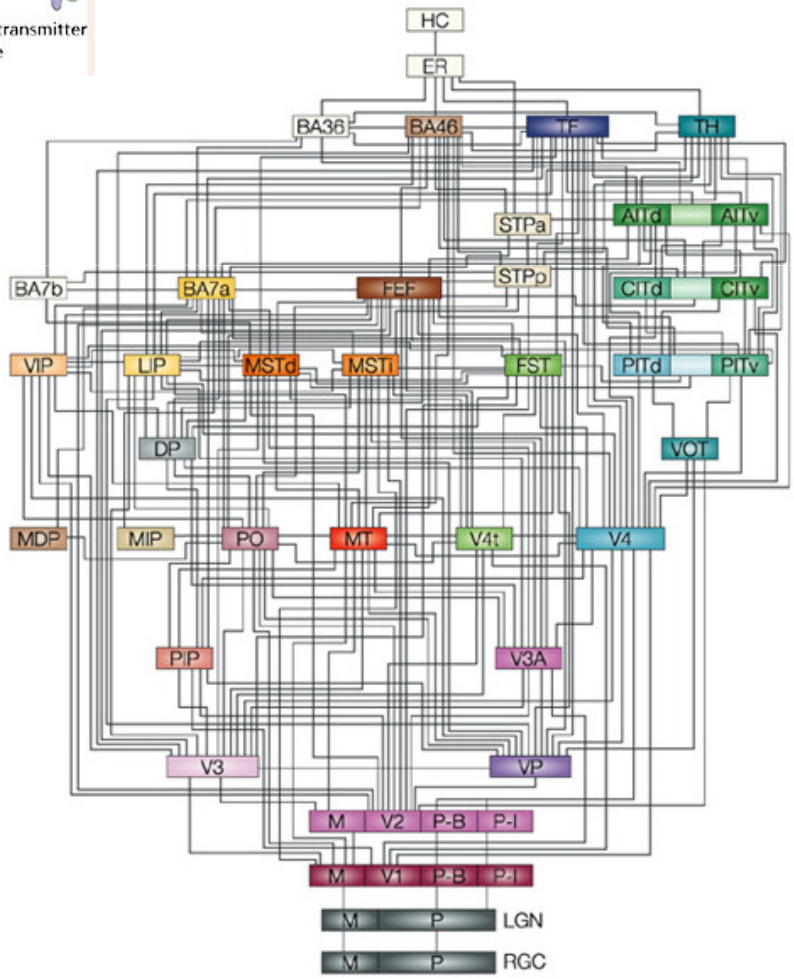


Figure 1 | **Types of mosaicism and patterns of cutaneous mosaicism.** The main types of mosaicism are somatic (**a**), gonosomal (**b**) and germline (**c**). Recognizable patterns of somatic mutations in the skin have been described. These include narrow lines of Blaschko (**d**), broad lines of Blaschko (**e**), checkerboard pattern (**f**), phylloid pattern (**g**) and patchy pattern without midline separation (**h**). The figure is modified, with permission, from REF. 9 © American Medical Association.


a
Somatodendritic
Axonal
Intracellular recording
Action potentials
Excitatory inputs
Kv4.2
Kv3 throughout dendrite
Proximal dendrites
Kv2.1
Soma
Kv1 JXPs
Nav, Kv1, Cav Presynaptic nerve terminals
EPSPs
Distal dendrites
HCN
Dendritic action potentials
Cav
Inhibitory inputs IPSPs
AIS Nav, KCNQ
Nodes of Ranvier Nav, KCNQ, Kv3.1b
Neurotransmitter release
Back propagation


1
2
3
4
5
6
CRC
α1
α2
α3
α5
DB
Large basket cell (CCK)
α1
α2
ais
α2
Ch
Large basket cell (PV+)
Ng
M
Thalamocortical afferents
Grey matter
White matter


HC
ER
BA36
BA46
TF
TH
STPa
AITd
AITv
BA7b
BA7a
FEF
STPp
CITd
CITv
VIP
LIP
MSTd
MSTl
FST
PITd
PITv
DP
VOT
MDP
MIP
PO
MT
V4t
V4
PIP
V3A
V3
VP
M
V2
P-B
P-I
M
V1
P-B
P-I
M
P
LGN
M
P
RGC

CONCLUSIONS

- The genetics of Epilepsy emerged as extremely complex.
- Susceptibility to common forms of epilepsy likely involve hundreds or thousands of rare alleles with a variable degree of penetrance and expressivity.
- At the clinical level, neurologists should recognize familial traits, which are indeed present among the bulk of sporadic cases.
- Identification of susceptibility/low penetrant alleles has limited clinical utility and inestimable impact on the understanding of epileptogenesis.