2023 GW Epilepsy Board Review & Best Practices

SPINAL FLUID ANALYSIS AND CHEMICAL AND METABOLIC SCREENING

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DISCLOSURES

- **Disclosure of Financial Relationships**
  Consultant – Neurocrine Biosciences
  Speaker Bureau – Zogenix, Inc and Marinus Pharmacueticals

- **Off-Label Usage**
  None

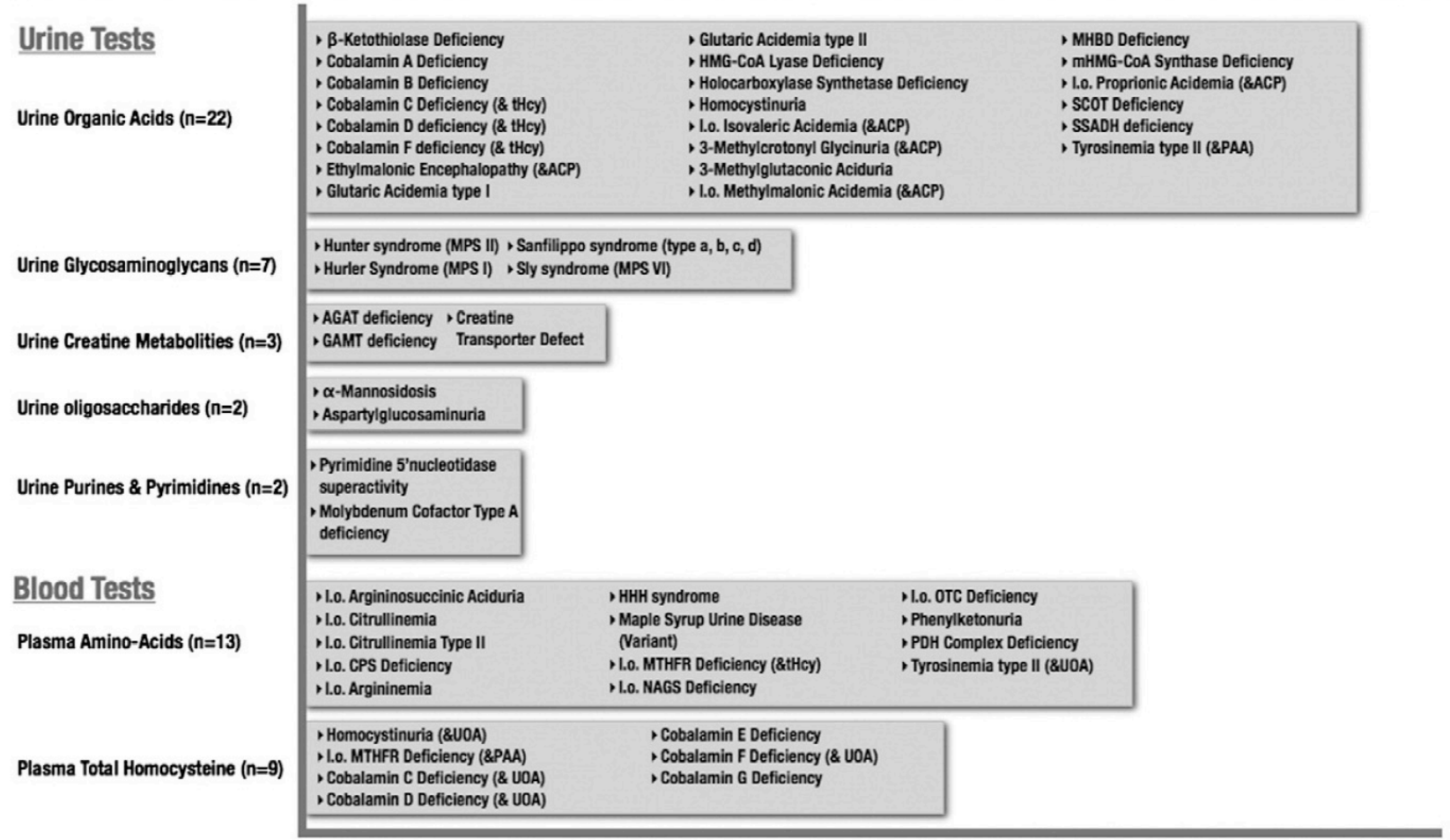
Chemical and Metabolic Screening

Spinal fluid analysis

IEM with seizures as a prominent feature

- Amino acid and organic acid disorders
- Glucose transport/ regulation disorders – GLUT1, HI/HA, DEND
- Hyperhomocysteinemia – cobalamin deficiencies, homocysteinuria, MTHFR deficiency
- Urea cycle disorders
- Fatty acid oxidation disorders
- Creatine synthesis/ transport disorders
- Neurotransmission – biopterin deficiencies, SSADH-D
- Sulfite oxidase deficiency
- Vitamins/ co-factors: biotinidase, cerebral folate, holocarboxylase, molybdenum cofactor, pyridoxine, thiamine
- Mitochondria – Co-Q10 deficiency, MELAS, PDH complex deficiency
- Metals - Menkes
- Lysosomal and peroxisomal disorders

Summary of all treatable IEM (n=50/62%) which can be detected by 'Metabolic Screening Tests', each of which is affordable and accessible with the potential to identify at least 2 IEM (and up to 22). Each bar represents the yield of the specific screening test, and lists the number and types of treatable IEM it can identify.



Legend *Abbreviations: plasma amino acids (PAA), total homocysteine (tHcy), plasma acylcarnitine profile (ACP), urine organic acids (UOA).*

For the mucopolysaccharidoses, enzyme activity should measured as a next step: Hurler (Iduronidase); Hunter syndrome (Iduronate-2-sulphatase); Sanfilippo syndrome (IIIa = Heparan-N-sulfatase, IIIb = N-acetyl-glucosaminidase, IIIc = Acetyl CoA glucosamine N-acetyl transferase, IIId = N-Acetyl-glucosamine-6-sulfatase); Sly syndrome= β-Glucuronidase)

Fig. 1. Bar graph depicting the yield of 'Metabolic Screening Tests'.

Lumbar puncture

- 5 Methyltetrahydrofolate
- Neopterin
- Tetrahydrobiopterin and Neopterin
- Neurotransmitter Metabolites (5HIAA, HVA, 3OMD)
- Pyridoxal 5-phosphate
- Succinyladenosine
- Sialic Acid
- Alpha-aminoadipic Semialdehyde
- CSF Glucose
- CSF Amino Acids
- CSF Lactate

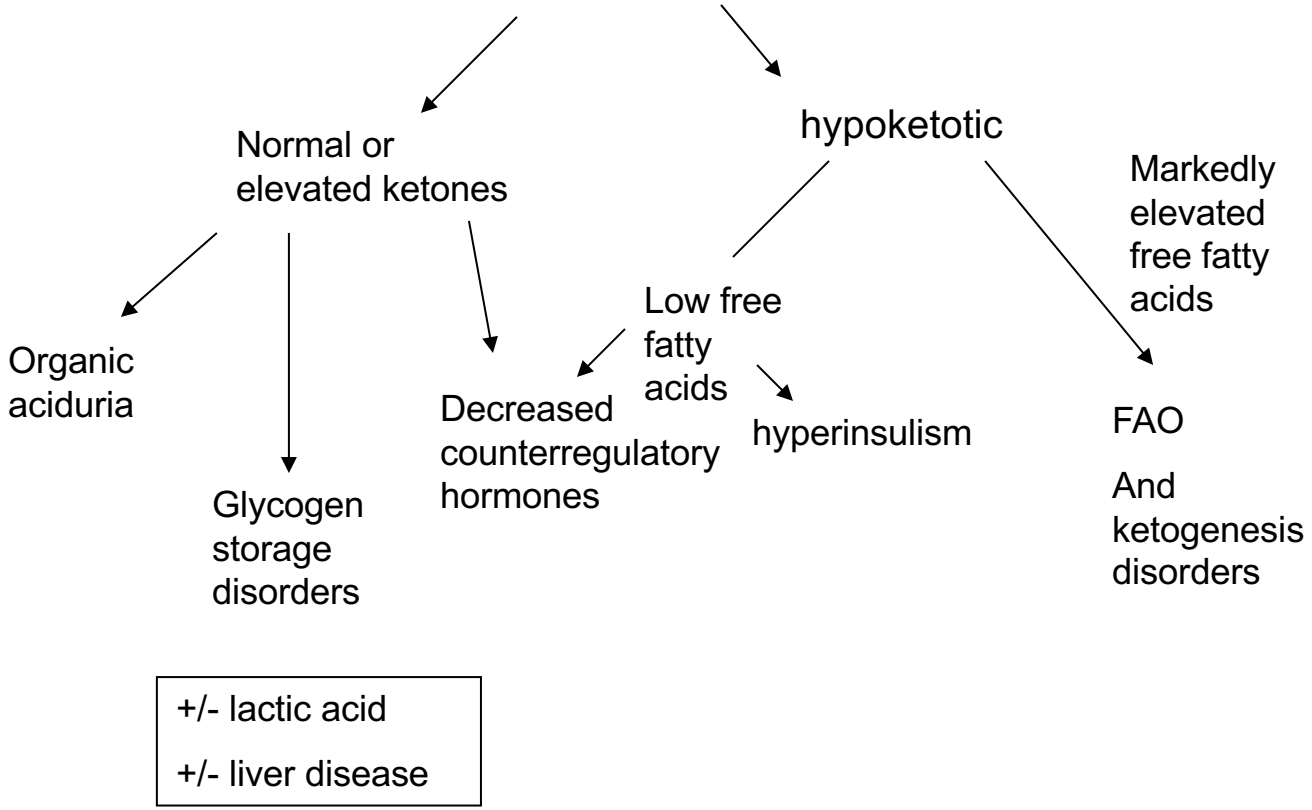
Types of disorders of intermediary metabolism- small molecule

- Aminoacidopathies
- Organic acidopathies
- Carbohydrate metabolism disorders (CDG, Glycogen storage disorders, fructose metabolism, galactosemia)
- Disorders of vitamin metabolism/ transport and cofactors (biotin, pyridoxine, folate, cobalamin…)
- Urea cycle disorders
- Fatty acid oxidation disorders
- Mitochondrial disorders (respiratory chain, carnitine disorders, pyruvate disorders)

Hypoglycemia

- Definition: blood glucose <45mg/dl
- Consider other causes (especially in neonate: SGA, maternal diabetes, sepsis, severe systemic illness), get history of last meal, examine clinically (hepatomegaly, liver failure, cirrhosis, small genitals, hyperpigmentation, short stature)

Hypoglycemia



Lab tests during symptomatic hypoglycemia

- Free fatty acids and 3-hydroxybutyrate (serum or plasma) and urinalysis for ketones.
- Acylcarnitine profile (plasma)
- Insulin and cortisol (serum)
- Lactate
- Organic acids (urine)
- One spare tube of serum or plasma
- Others: blood gases, CBC, lytes, LFTs, uric acid, triglycerides, GH, ammonia (liver damage), plasma AA, toxicology (C-peptide)

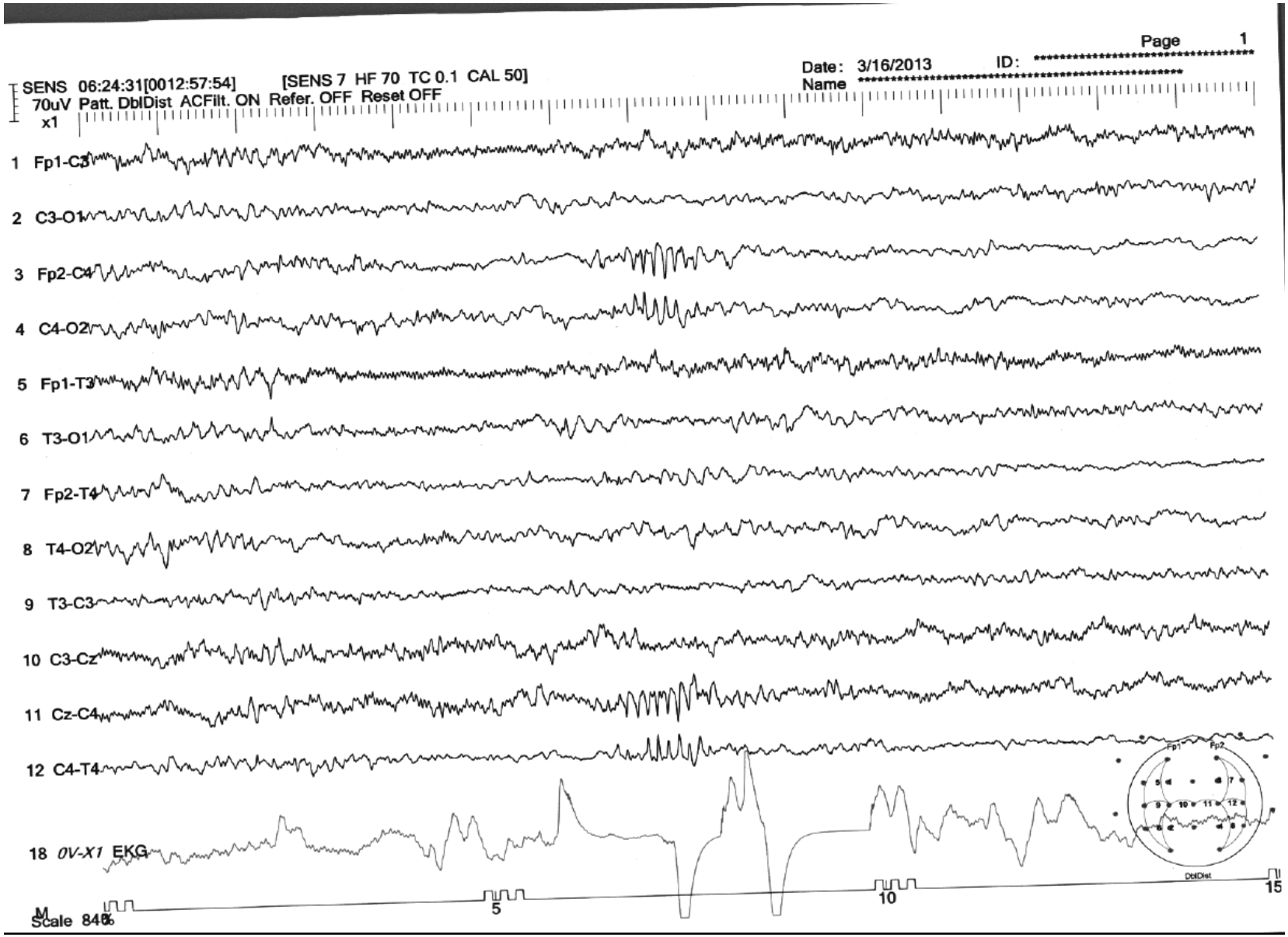
Hypoglycemia

- **Ketones** “normal” (low) or insufficiently elevated
  - **Free fatty acids relatively low**: hyperinsulinism, decreased counterregulatory hormones (eg hypopituitarism)
  - **Free fatty acids greatly elevated**: disorders of FAO and ketogenesis
- **Ketones** elevated “ketotic hypoglycemia” = organic acidurias, decreased counterregulatory hormones, glycogen storage diseases types III and 0
- **Lactate elevated** (>2mmol/l)
  - Without **hepatomegaly** Organic acidurias, ketolysis defects, respiratory chain defects, long chain fatty acid oxidation disorders (especially LCHAD)
  - Isolated **hepatomegaly** Glycogen storage diseases, gluconeogenesis defects
- **Liver disease** Fructose intolerance, respiratory chain defects, long chain FAO disorders, tyrosinaemia type 1

Select Amino Acid and Organic Acid Disorders Associated with Seizures

- Amino acids
  - MSUD
  - Phenylketonuria
  - Non-ketotic hyperglycinemia
- Cerebral organic acidopathies
  - Glutaric acidemia I
  - Canavan disease (NAA)
  - SSADH Deficiency
- Systemic Organic acidopathies
  - Methylmalonic academia
  - Propionic acidemia
  - Isovaleric acidemia
  - HMG CoA lyase deficiency

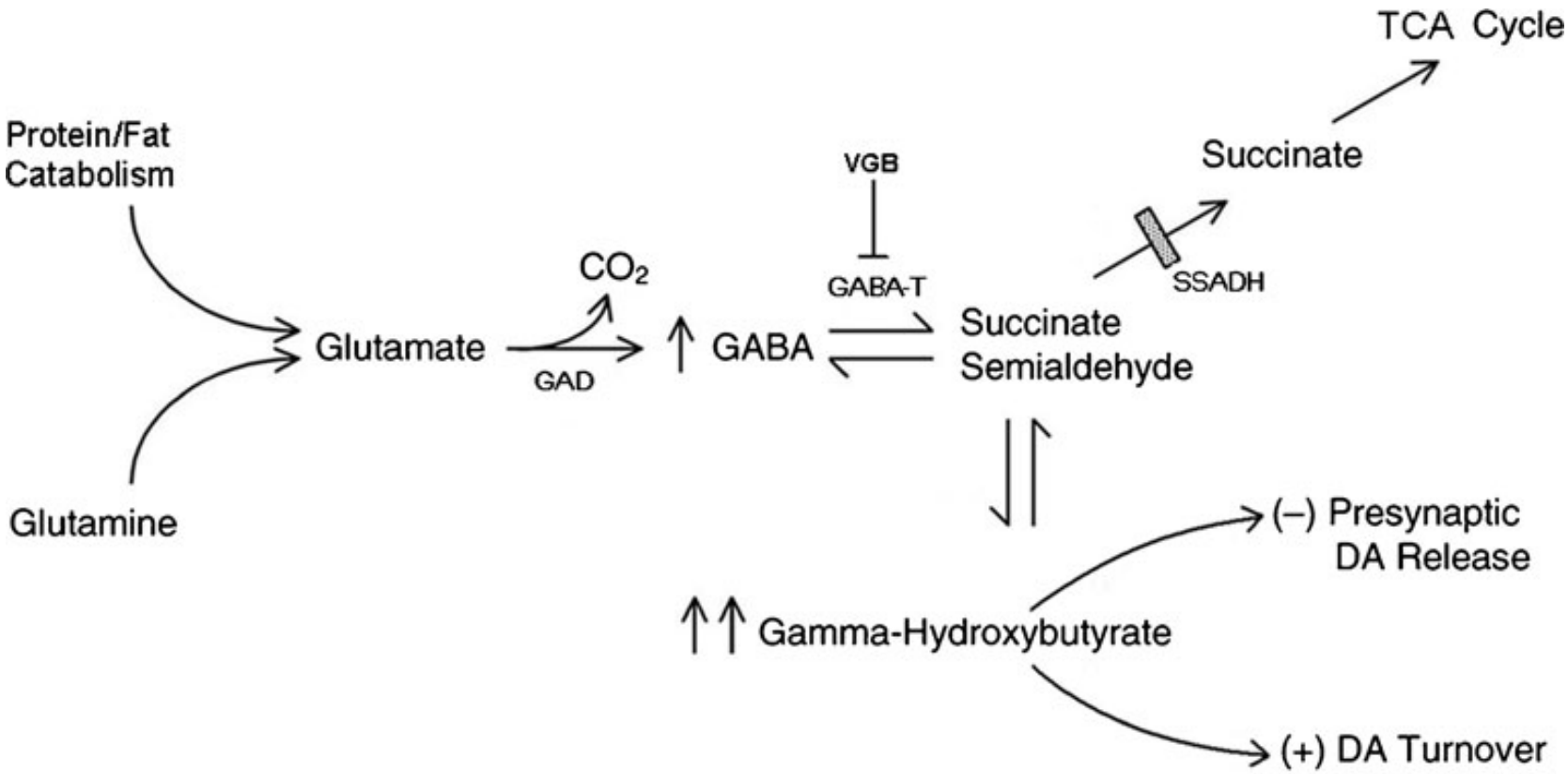
Neonatal encephalopathy and seizures - MSUD



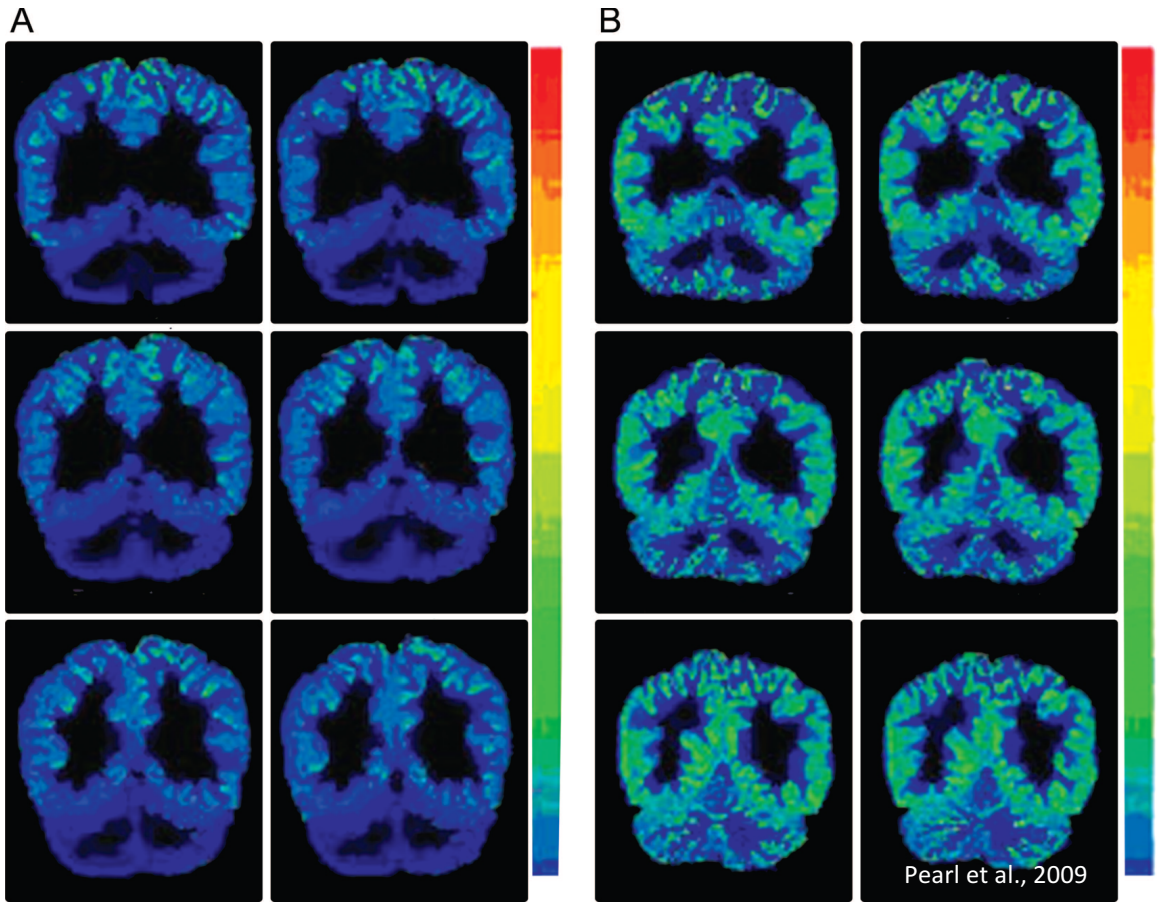
Glycine Encephalopathy (NKH)

- High CSF > plasma glycine
- Usually neonatal or infantile onset seizures
- Treatment – glycine restriction +/- benzoate, NMDA antagonists

SSADH Deficiency



[11C]-flumazenil PET scans in an affected subject (A) and the subject's parent (B) showing marked reduction of cortical binding potential in A



Pyridoxine-dependent seizures

- ALDH7A1 mutations – encodes α-amino adipic semialdehyde dehydrogenase (antiquitin)
- Diagnosis – increased AASA in urine or plasma; genetics
- Pyridoxine 100 mg IV while on EEG
- Some may also have pyridoxine-responsive seizures (and do not necessarily depend on pyridoxine)
- Pyridoxine 5'-phosphate oxidase deficiency (*PNPO*) – responds to pyridoxal phosphate
- PLP homeostasis protein (*PLPBP), ALPL, ALDH4A1*
- Treatment:
  - Pyridoxine 15-18 mg/kg/day up to 30 mg/kg/day (maximum 500 mg); others may be responsive to folinic acid 3-5 mg/kg/day
  - Pyridoxal phosphate 30-50 mg/kg/day for *PNPO*

Biotinidase deficiency

- Inability to cleave biocytin
- Presents 3-6 months old (when prenatal biotin stores are depleted) with developmental delay, hypotonia, seizures, ataxia, sensorineural hearing loss, optic atrophy, and rash
- Treatment – biotin 10 mg/day
- Multiple carboxylase deficiency presents at birth (inability to load biotin onto carboxylases)

Creatine synthesis and transporter deficiencies

- GAMT and AGAT deficiency, creatine transporter deficiency (*SLC6A8*)

Tetrahydrobiopterin Deficiencies

- Often high phenylalanine; BH4 (tetrahydrobiopterin) is essential in synthesis of monoamine neurotransmitters
- GTPCH, **PTPS***, PCD, **DHPR***, SR deficiencies
  - ID, epilepsy* (often myoclonic), extrapyramidal symptoms

Cerebral Folate Deficiency

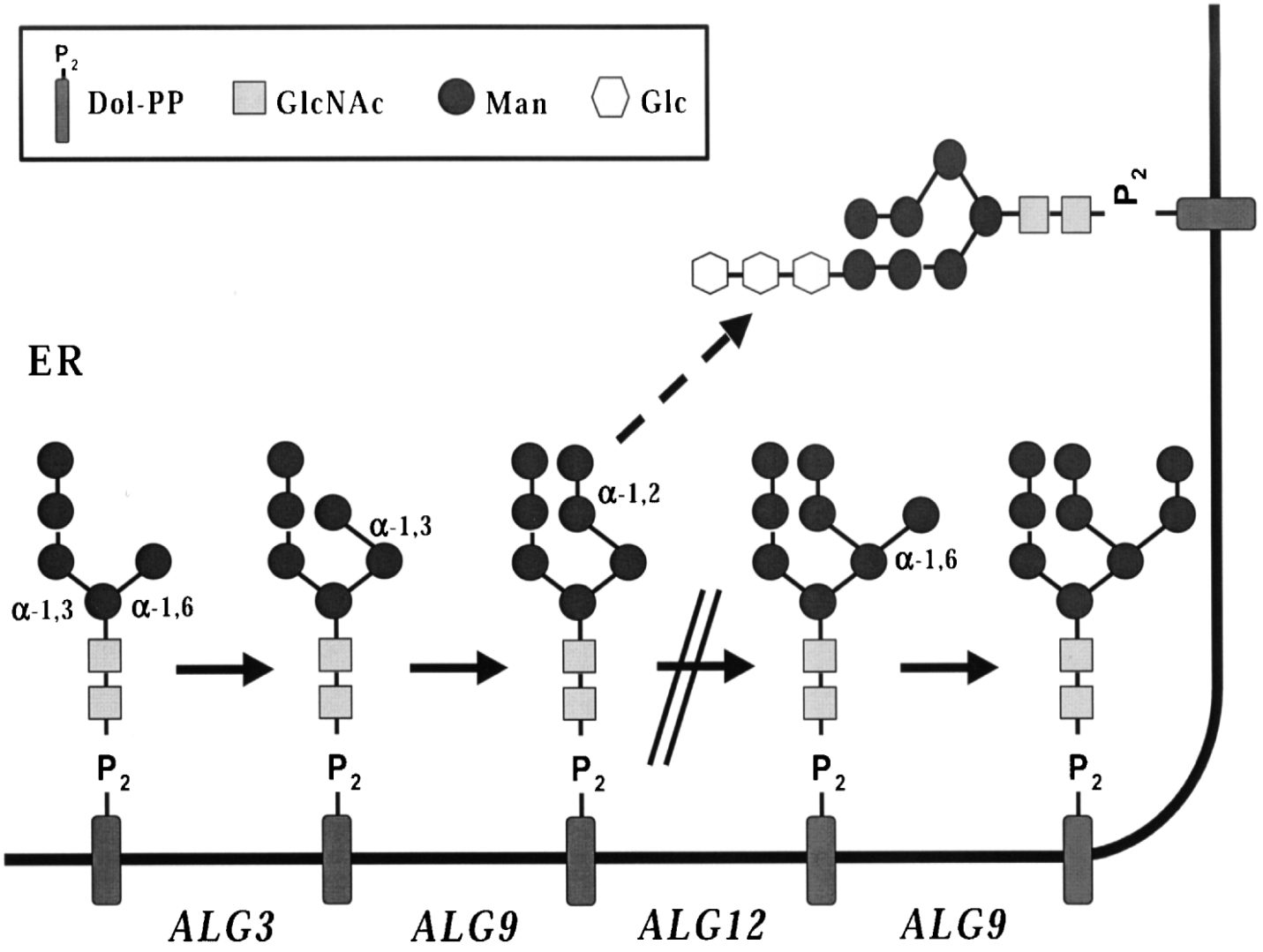
- Antifolate receptor antibodies or folate receptor gene mutations
- infantile onset irritability, cranial growth deceleration, seizures, pyramidal and extrapyramidal tract deficits
- Treatment – folinic acid

Serine biosynthesis disorders

  - Diagnosis – low serine in plasma or CSF
  - Congenital microcephaly and psychomotor regression
  - Treatment – serine 400-600 mg/kg/day and glycine 200-300 mg/kg/day)

Congenital disorders of glycosylation

- Also known as carbohydrate deficient glycoprotein syndromes, are a collection of disorders in which many glycoproteins are deficient or have reduced carbohydrate side chains
- Many subtypes of congenital disorders of glycosylation have been described based on the isoelectric focusing patterns of transferrin and on clinical features
- Any block in the synthesis of these side chains will result in an undersialylated transferrin molecule
- Because it is a major serum protein and is easily detectable, transferrin is utilized as a marker in screening for congenital disorders of glycosylation


P2
Dol-PP
GlcNAc
Man
Glc
ER
α-1,3
α-1,6
α-1,3
α-1,2
α-1,6
P2
P2
P2
P2
P2
P2
ALG3
ALG9
ALG12
ALG9

Clinical features of CDGs

- Failure to thrive
- Hyptonia
- Inverted nipples
- Unusual fat deposits
- Mental and psychomotor retardation
- Stroke-like episodes
- Protein losing enteropathy
- Hypoglycemia
- Generalized dysmyelinization
- Optic atrophy
- Peripheral neuropathy
- Coagulopathy
- Seizures

Case 1

- 2 year old girl presents with staring spells, lasting approximately 10 seconds, multiple times throughout the day
- EEG shows generalized 3.5 Hz spike-wave discharges
- She fails treatment with adequate doses of ethosuximide, valproic acid, and lamotrigine

Glucose Transporter Deficiency

- Presents with developmental delay, refractory generalized epilepsy (early), and/or various movement disorders
- Diagnosis
  - Low CSF:plasma glucose (CSF glucose typically < 40)
  - *SCL2A1*
- Treatment
  - Ketogenic diet

GLUT1 Deficiency Syndrome

Early onset absence epilepsy: 1 in 10 cases is caused by GLUT1 deficiency

*Todor Arsov, *†Saul A. Mullen, *John A. Damiano, *Kate M. Lawrence, ‡Linda L. Huh, §Melinda Nolan, ¶Helen Young, #Anaïs Thouin, *Hans-Henrik M. Dahl, *Samuel F. Berkovic, **Douglas E. Crompton, ††Lynette G. Sadleir, and *†‡‡Ingrid E. Scheffer

- 11/89 with early onset absence epilepsy (age < 4 yrs) had GLUT1 deficiency
- Early onset absence epilepsy defined as onset of absences before age 4 years, generalized spike waves > 2.5 Hz, no evidence of secondary cause, and absence of atonic-tonic seizures

Arsov et al. *Epilepsia* 2012.

GLUT1 and Absence Epilepsy

- Early-onset epilepsy (age < 3yrs)
- Diagnosis/ Clinical Aspects
  - Pure (n=111)
    - normal neurologic state and development, typical absence seizures and EEG
    - earlier initial seizure control and better seizure-free survival curve
  - Non-pure (n=77)
- Findings
  - Pure: *no mutations in SLC2A1 or abnormal neuroimaging*
  - Non-pure
    - *4 with SLC2A1 mutations and 21 with abnormal neuroimaging*

Agostinelli et al. *Epilepsia* 2013: 1761-1770.

Urea cycle disorders

- The urea cycle is the metabolic process by which the body gets rid of nitrogen, and is the source of endogenous arginine, ornithine, and citrulline
- There are six enzymes and two transporters that take part in this process
  - A deficiency of any one of them upsets the process and causes excess nitrogen, in the form of ammonia, to accumulate in the body
  - All autosomal recessive except OTC deficiency which is X-linked
  - Urea cycle disorders:
    - carbamoylphosphate synthetase I (CPS1) deficiency
    - ornithine transcarbamylase deficiency (OTC) (most common type)
    - argininosuccinic acid synthetase deficiency (ASS1) (also called citrullinemia)
    - argininosuccinase acid lyase deficiency (ASL)
    - arginase deficiency (ARG1)
    - n-acetylglutamate synthetase deficiency (NAGS) (cofactor)
    - ornithine translocase deficiency (ORNT1)
    - citrin deficency

Urea cycle disorders

- Severe deficiency in 1st four enzymes (CPS1, OTC, ASS1, and ASL) or cofactor producer (NAGS) results in early presentation
  - Full term infants who are well for the first 24-48 hours develop lethargy, vomiting, alkalosis, hyperventilation, hypothermia
  - Appear septic
  - Elevated ammonia, respiratory alkalosis
- Milder deficiencies and deficiencies in other enzymes/ transporters result in milder symptoms later in life (vomiting, lethargy, behavior change, sleep disorders, liver disease), often triggered by stress/ illness
- Therapy
  - Dialysis, nitrogen scavengers (sodium phenylacetate and sodium benzoate), arginine and/or citrulline
  - Restrict nitrogen – diet (protein restriction but ensuring appropriate amino acid levels)
  - Treat catabolic state

Fatty Acid Oxidation (FAO) Disorders

- FAO occurs in the mitochondria which are impermeable to acyl-CoA esters > 12-14 carbons (transported through carnitine cycle)
- Symptoms – seizures, encephalopathy, emesis, hypotonia, exercise intolerance, muscle disease, cardiac disease presenting at various ages; exacerbations during fasting or higher energy demands
- Types:
  - Carnitine cycle - primary carnitine deficiency (carnitine uptake defect); CPT I, CPT II, and CACT deficiencies
  - VLCAD, LCAD, MCAD, SCAD, SCHAD, TFP deficiencies, others
  - Glutaric acidemia type II (multiple acyl-CoA dehydrogenase deficiency)
- Screening/ Diagnosis – carnitine, acylcarnitines, urine organic acids, urine acylglycines, free fatty acids
- Treatment – glucose, avoidance of fasting, carnitine in some

Mitochondrial Disorders

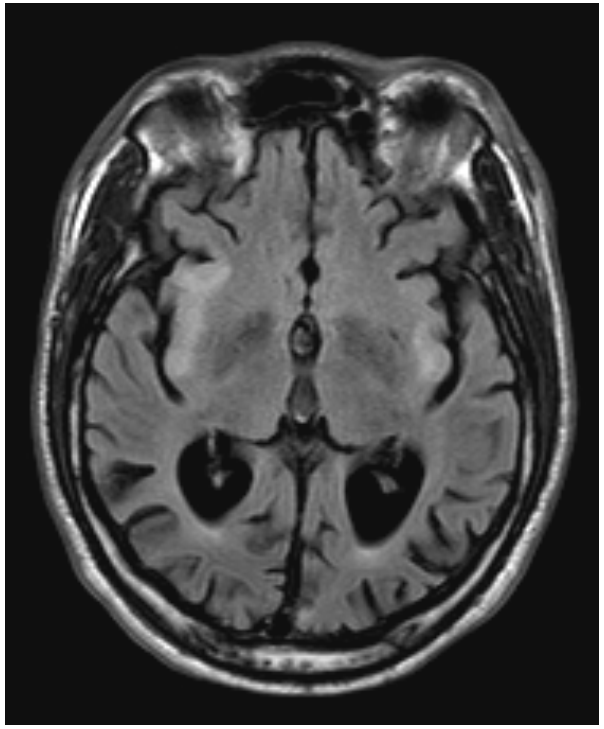
- Neurological symptoms due to injury, mitochondrial dysfunction, oxidative stress, energetic failure
- MELAS, Leigh syndrome, MERRF, POLG mutations, ataxia neuropathy syndromes, CPEO, Kearns-Sayre syndrome, NARP (neurogenic weakness with ataxia and retinitis pigmentosa), MEMSA (myoclonic epilepsy myopathy sensory ataxia), others
- Diagnosis – lactic acid, neuroimaging, ETC, muscle biopsy, genetic
- Due to defects of nuclear DNA or mitochondrial DNA
  - mtDNA maintenance, mitochondrial protein synthesis, CoQ10 biosynthesis, respiratory chain complexes
- Treatment – variable, but generally avoid valproic acid; arginine for MELAS

Mitochondrial encephalopathy with lactic acidosis & stroke (MELAS)

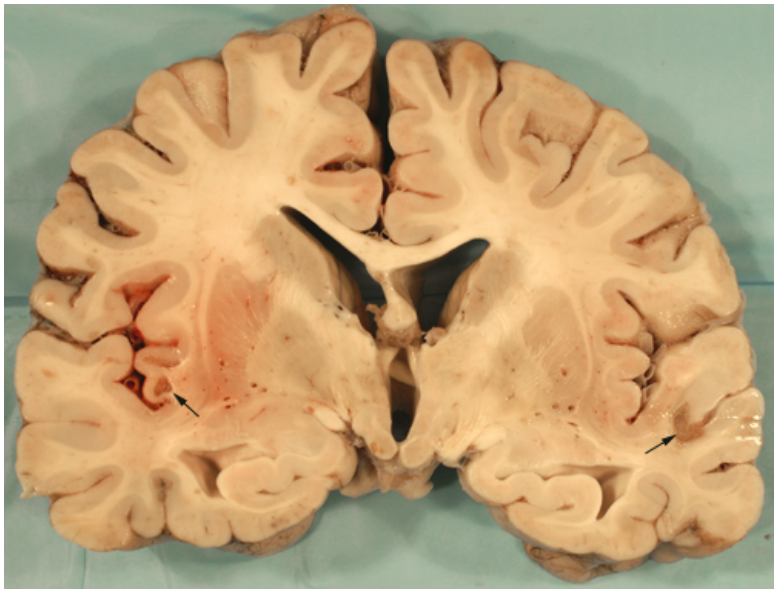
- **M**itochondrial **e**ncephalomyopathy, **l**actic **a**cidosis, and **s**troke-like episodes
- M.3243A>G pathogenic variant (80%) (tRNA)
- Usually seen in children and young adults
- Seizures, severe headache, vision abnormalities, dementia
- CNS: infarct-like lesions in cortex, subcortical white matter & cerebellum; Ca^{++} in BG
- Muscle: “ragged red fibers”

MELAS

CNS findings

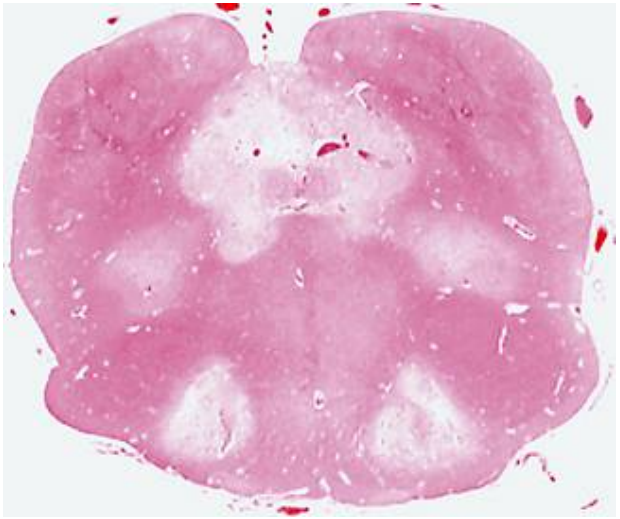


Insular FLAIR abnormality



Small infarcts

Leigh syndrome



- Subacute necrotizing encephalopathy
- Mostly occurs in childhood
- >75 nuclear and mtDNA genes, mostly complex I and IV
- Dysphagia, hypotonia, ataxia, peripheral neuropathy, abnormal eye movement
- Necrotizing lesions in midline structures

http://www.neuropathologyweb.org

Lysosomal storage diseases

- Sphingolipidoses
  - Neuronal lipidosis
  - Tay-Sachs disease
  - Neimann-Pick disease
  - Leukodystrophies
    - Krabbe disease
    - Metachromatic leukodystrophy
  - Histiocytosis: Gaucher disease
- Mucopolysaccharidoses
- Glycogenosis type II (Pompe): myopathic

Neuronal lipidosis

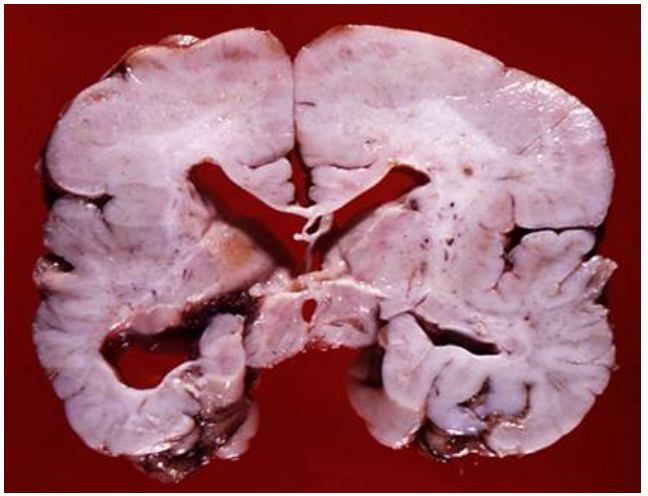
- Clinical presentation: neurological regression, seizures, blindness
- GM1 gangliosidosis
  - Autosomal recessive
  - Deficiency of **β-galactosidase**
  - Early Infantile, late infantile, juvenile, and adult forms
- GM2 gangliosidosis (Tay-Sachs, 'most common')
  - Autosomal recessive - *HEXA*
  - Deficiency of **hexosaminidase A**
  - Infantile, juvenile, and adult forms
- Niemann-Pick disease
  - Type A & B: deficiency of **sphingomyelinase**
  - Type C: cholesterol storage disease

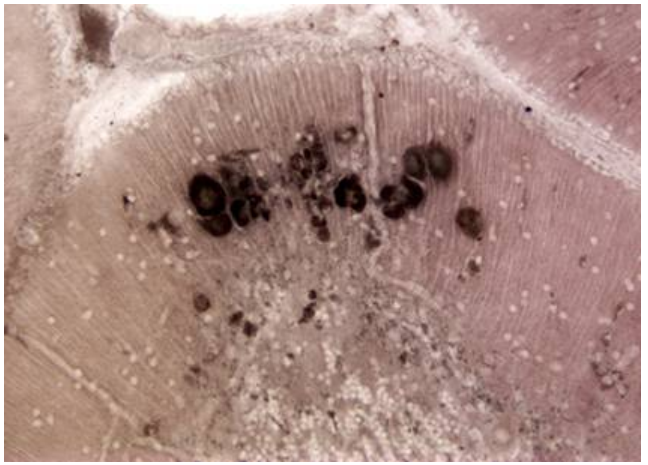
THE MOST COMMON LSDs

LSD	DEFICIENT ENZYME	PHENOTYPE
SPHINGOLIPIDOSES		
GM1 gangliosidosis	b-galactosidase	neuronal lipidosis mucopolysaccharidosis
GM2 gangliosidosis (Tay-Sachs disease)	hexosaminidase A	neuronal lipidosis
Niemann-Pick Disease	sphingomyelinase	neuronal lipidosis storage histiocytosis
Globoid cell leukodystrophy (Krabbe dis)	galactocerebrosidase	leukodystrophy
Metachromatic leukodystrophy	arylsulfatase A	leukodystrophy
Gaucher disease	glucocerebrosidase	storage histiocytosis
MUCOPOLYSACCHARIDOSES	glycosaminoglycan cleaving enzymes	mucopolysacccharidosis
GLYCOPROTEINOSES	glycoprotein cleaving enzymes	mucopolysacccharidosis
GLYCOGENOSIS TYPE II (POMPE DISEASE)	a-glucosidase	skeletal and cardiac myopathy
NEURONAL CEROID LIPOFUSCINOSES	lysosomal proteases	neuronal lipidosis

Zellweger syndrome

- Phenotypic spectrum of peroxisome absence (Zellweger spectrum disorders)
- PEX genes (13 known)
- Dysmorphic features, hypotonia, eye abnormalities, hepatomegaly, renal cysts
- Neuronal migration defects & white matter abnormalities
- Diagnosis: VLCFAs, phytanic & pristanic acids, plasmalogens, pipecolic acid (plasma/ urine)





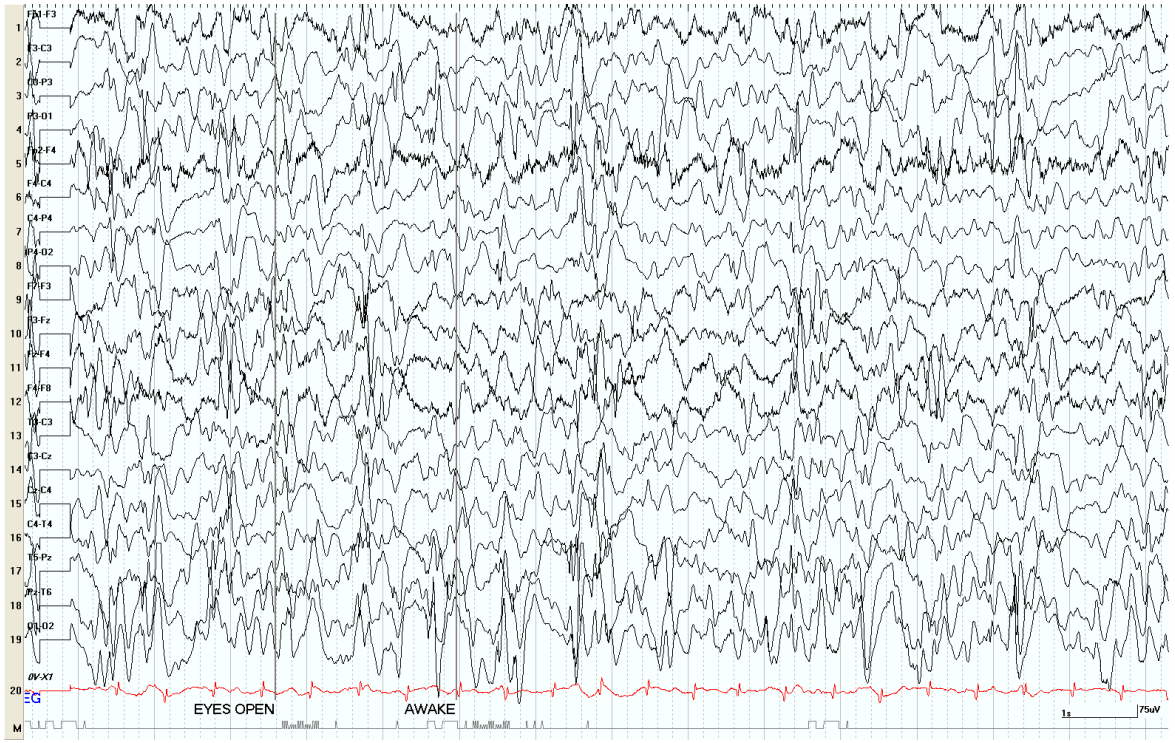
Adrenoleukodystrophy (ALD)

- Rare, genetic disorder characterized by the breakdown or loss of the myelin sheath surrounding nerve cells in the brain
- Progressive dysfunction of the adrenal gland
- X linked recessive; *ABCD1* – encodes an ATPase binding cassette protein involved in peroxisomal beta-oxidation
- Accumulate high levels of saturated, very long chain fatty acids in the brain and adrenal cortex because the fatty acids are not broken down by an enzyme in the normal manner
- 1:20,000-1:50,000 (2-5 born per year in Virginia)

Clinical forms of ALD

- Classic childhood cerebral form (35%)
  - most severe and affects only boys, presents between ages 4 and 8
  - Features of this form may include visual loss, learning disabilities (ADHD), seizures, dysarthria (poorly articulated speech), dysphagia (difficulty swallowing), deafness, disturbances of gait and coordination, fatigue, intermittent vomiting, melanoderma (increased skin pigmentation), and progressive dementia
- The most common symptoms are usually **behavioral changes** such as abnormal withdrawal or aggression, poor memory, and poor school performance

Case 2



11 month old boy presents with clusters of flexor spasms and developmental regression

Question 2

- What test has the highest diagnostic yield in infantile spasms with a normal MRI brain and lack of physical exam features of tuberous sclerosis or trisomy 21?
  - CSF neurochemistry
  - MR spectroscopy
  - Karyotype
  - Chromosome microarray
  - Laboratory evaluation for inborn errors of metabolism

How should children with West syndrome be efficiently and accurately investigated? Results from the National Infantile Spasms Consortium

*Elaine C. Wirrell, †Renée A. Shellhaas, ‡Charuta Joshi, §Cynthia Keator, ¶Shilpi Kumar, #Wendy G. Mitchell, and Pediatric Epilepsy Research Consortium (PERC)[!]

Epilepsia, 56(4):617–625, 2015
doi: 10.1111/epi.12951

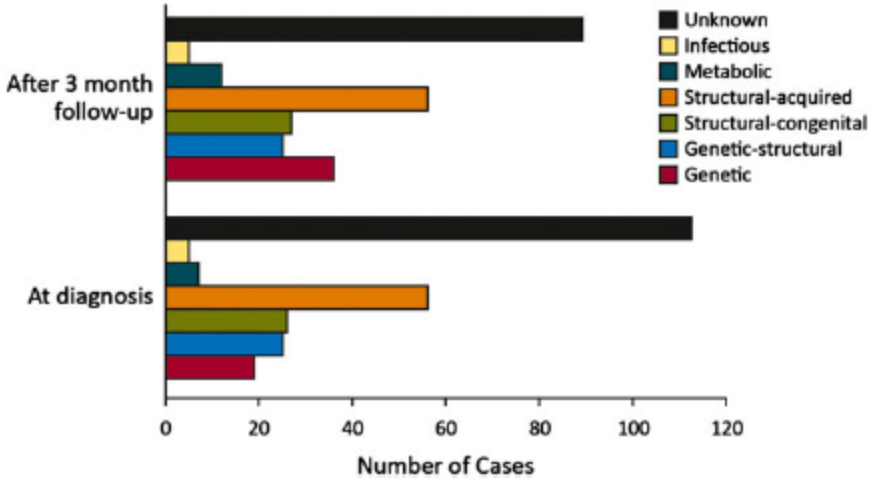


Figure 1.
Etiological Class at diagnosis, and after 3 months of follow-up.
Epilepsia © ILAE

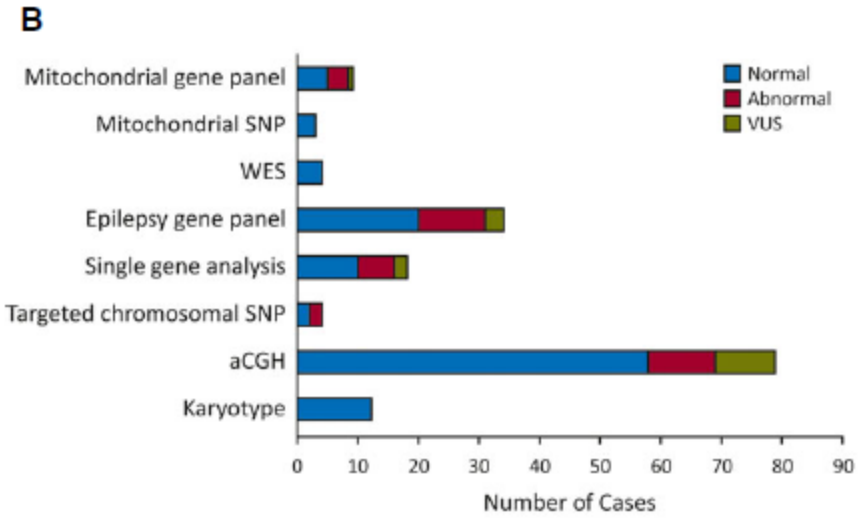


Figure 2.
Yield of genetic testing. (**A**) Prior to diagnosis of spasms. (**B**) Entire cohort; within 3 months after diagnosis of spasms. (**C**) Children without obvious cause at diagnosis.

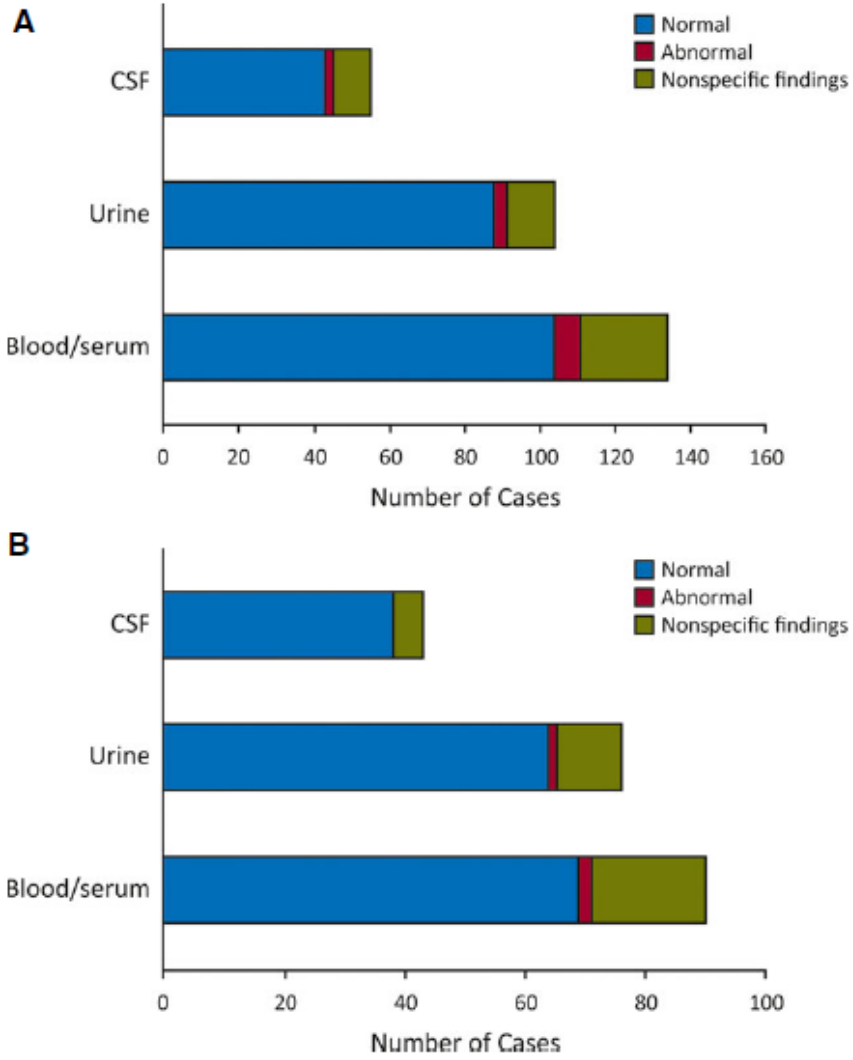


Figure 3.

Yield of metabolic testing. (**A**) Entire cohort; testing done prior to spasm onset or within first 3 months after diagnosis. (**B**) Children without obvious cause at diagnosis.

Recommendations for testing in newly diagnosed West syndrome (Wirrell et al, 2015)

- History and physical exam
- MRI brain
- If no obvious cause is identified:
  - Chromosome microarray

  - Epilepsy gene panel, serum lactate, serum amino acids, urine organic acids

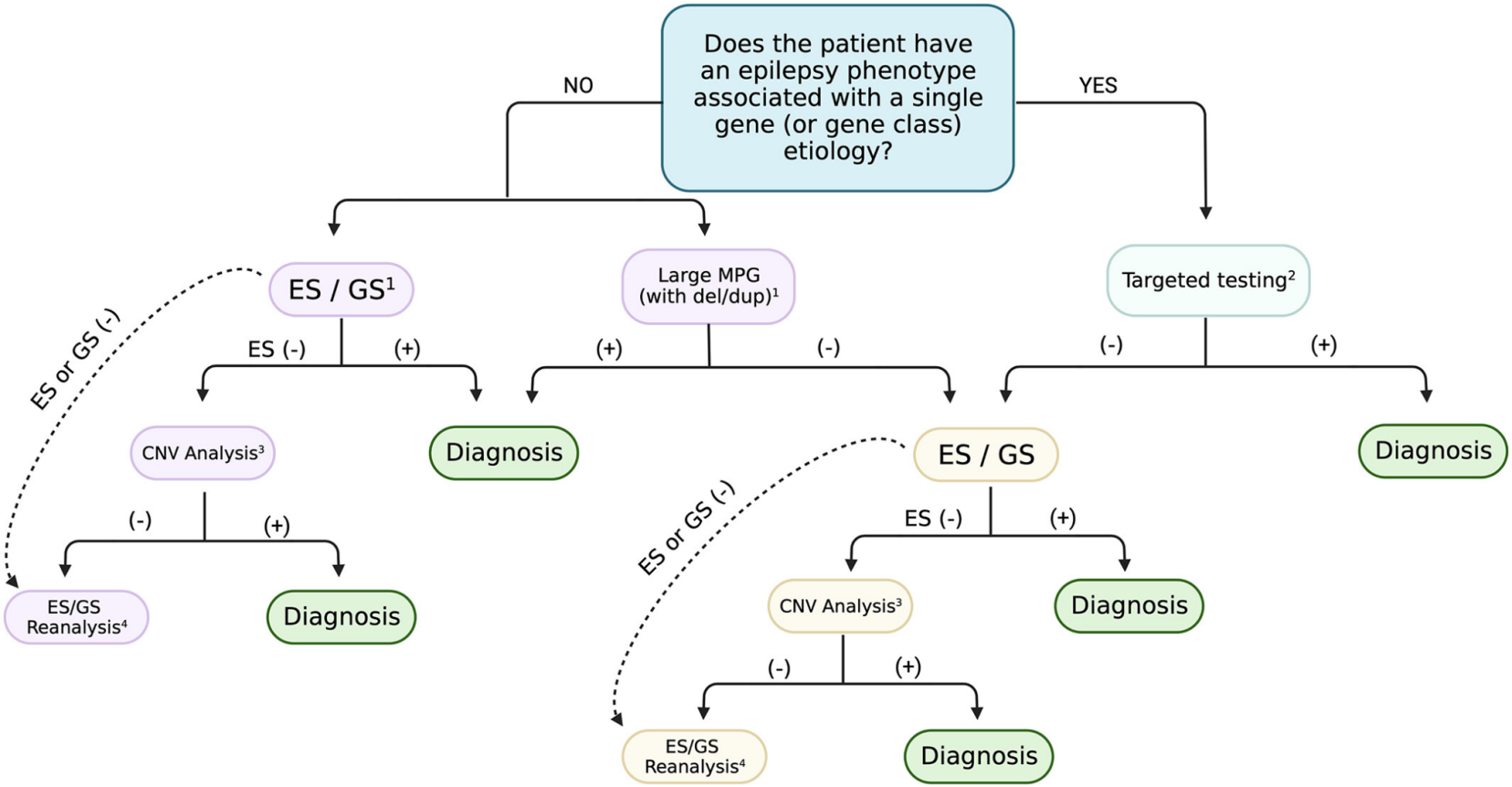
  - Consider whole exome sequencing

Journal of Genetic Counseling

PRACTICE GUIDELINE | Free Access

Genetic testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors

Lacey Smith, Jennifer Malinowski, Sophia Ceulemans, Katlin Peck, Nephi Walton, Beth Rosen Sheidley, Natalie Lippa



GENETIC ANALYSIS

John M. Schreiber, MD
Medical Director, EEG
Children's National Health System

Objectives

Discuss the rationale and clinical indications for genetic testing in Epilepsy

Review test methodology and limitations for genetic tests including chromosome microarray and next generation sequencing

Understand how to interpret test results in context

Provide examples of specific disorders where a positive result may influence treatment

Recognize the impact of genetics on response to medications

Genetic Basis of Epilepsy

- Risk for epilepsy is increased 2-4 times in first degree relatives of people with epilepsy of unknown cause
  - Annegers et al., 1982; Ottman et al., 1996
- Higher concordance in monozygotic than dizygotic pairs
  - Corey et al., 1991; Berkovic et al., 1998; Kjekdsen et al., 2003; Vadlamudi et al., 2004

Early approaches to Epilepsy Genetics

- Linkage analysis and positional cloning
  - Primarily identified genes encoding subunits of ion channels in families with epilepsy exhibiting Mendelian (usually autosomal dominant) inheritance patterns
- Genome-wide association studies (GWAS)
  - Intended to detect genetic variants (usually SNPs) more common in people with “complex genetic” epilepsy where patients usually have no affected relatives
  - “Common disease, common variant”
  - Effects of variants have been modest and causal variants are difficult to identify
  - Largely failed, possibly because variants are rare, but not very rare
- Copy Number Variants (CNVs)
  - Array CGH (comparative genomic hybridization)
  - SNP array

Epilepsy gene discovery

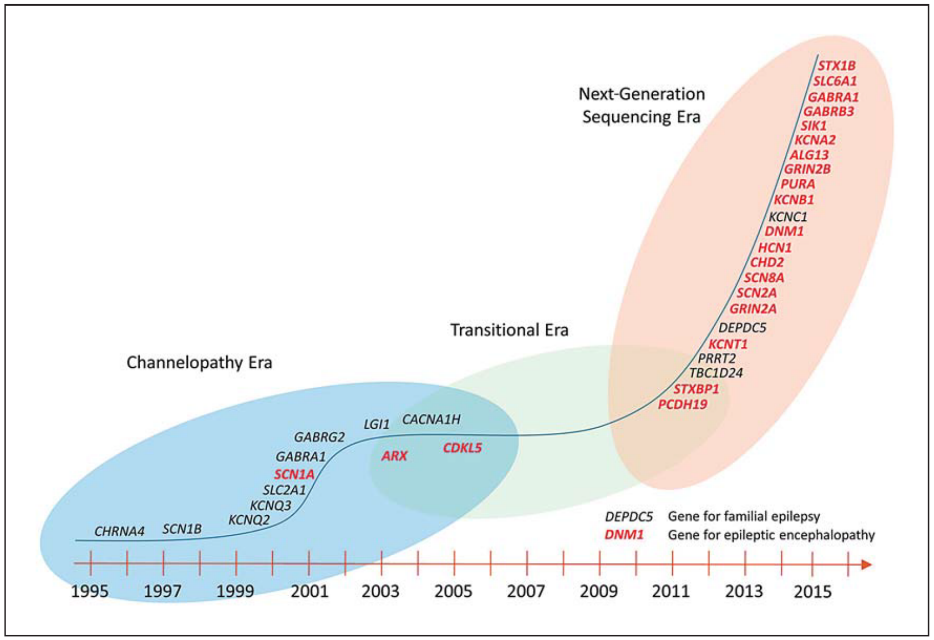
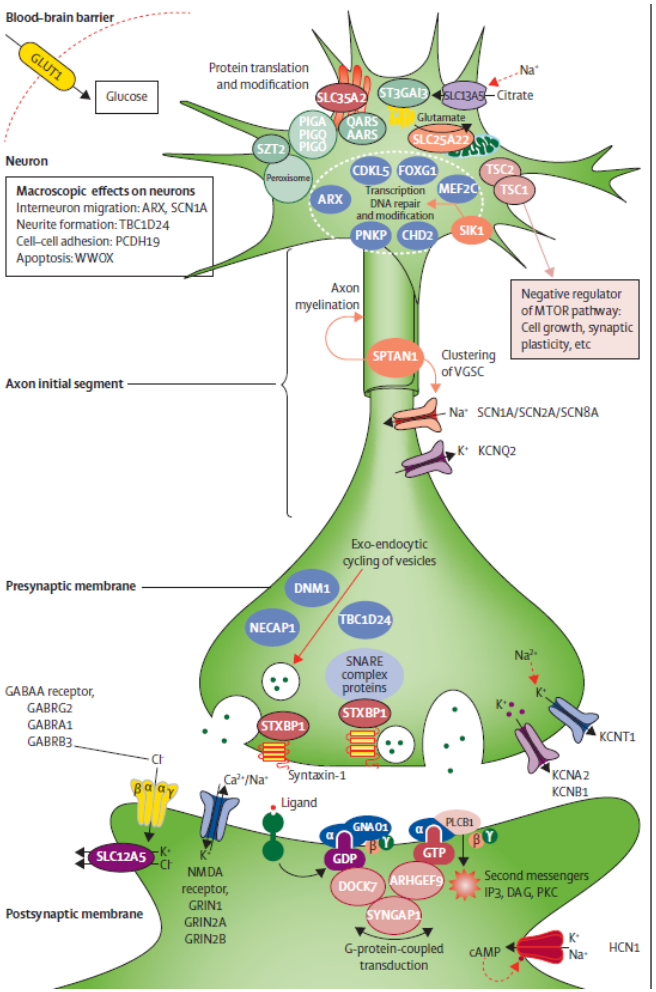


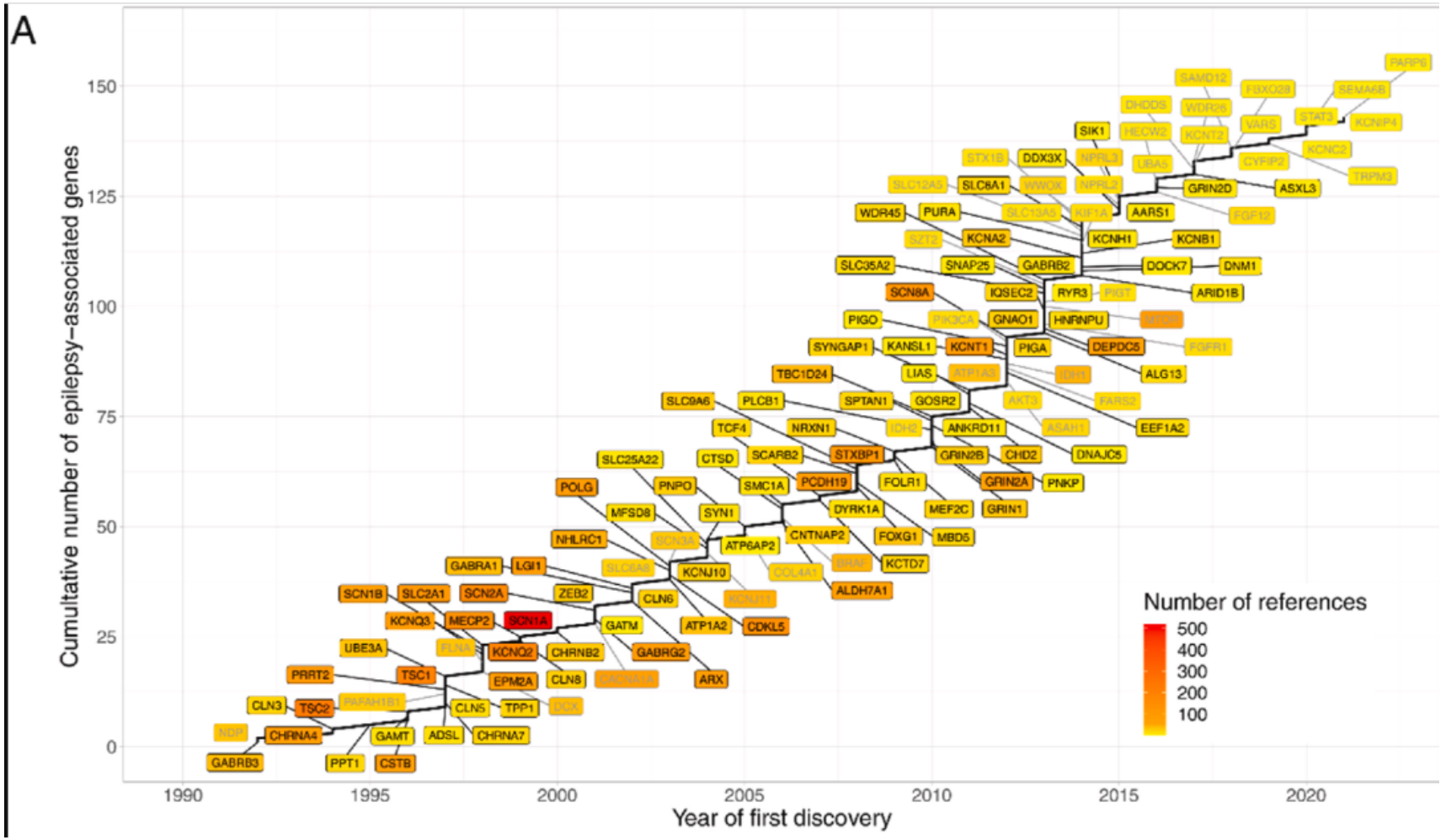
Fig. 2. Timeline of gene discovery in human epilepsies.

Mol Syndromol 2016;7:172–181



Lancet Neurol 2016; 15: 304–16

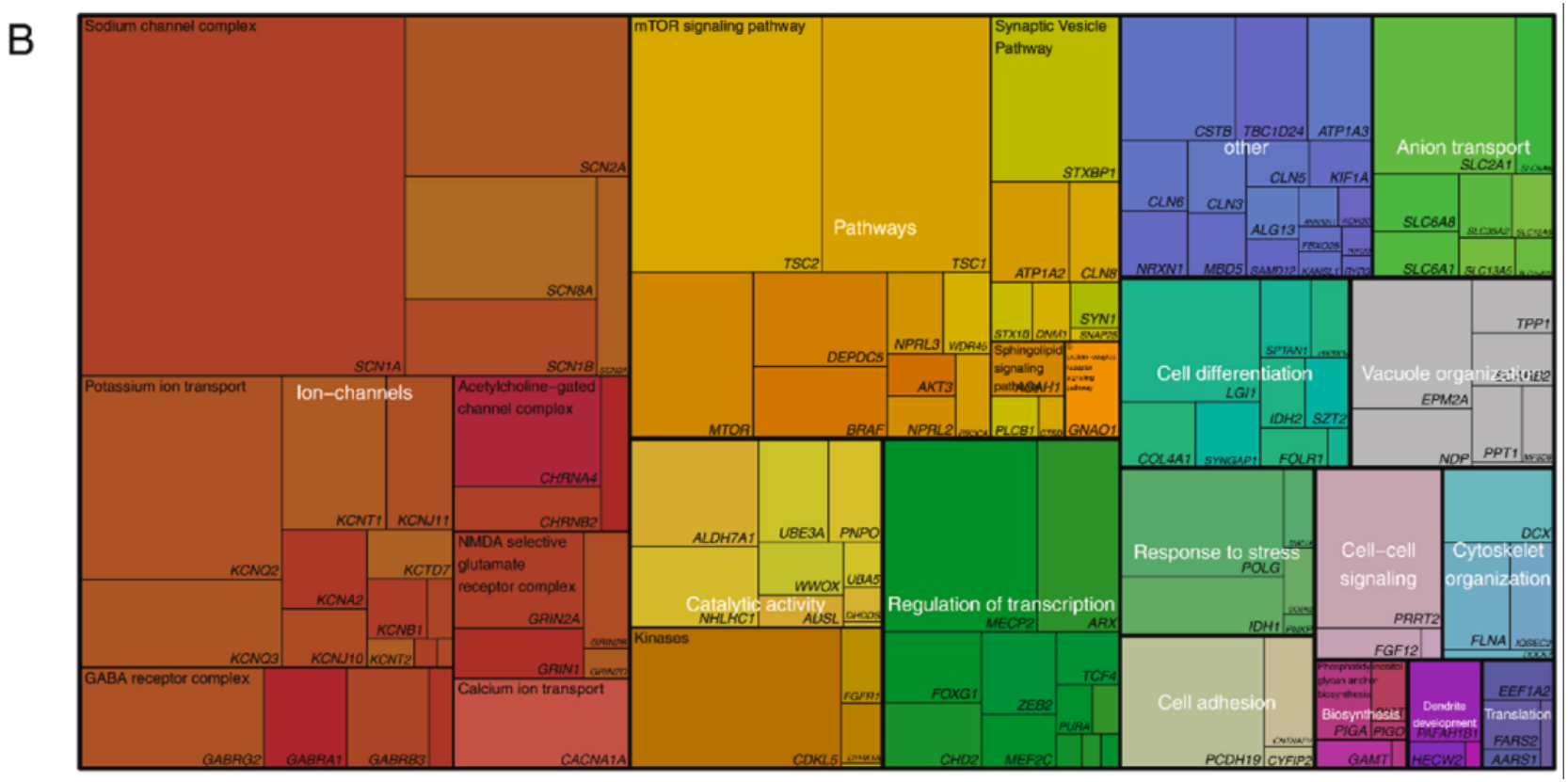
“Tier 1”* epilepsy genes



*mentioned at least once per year since discovery

Macnee et al., 2023

Proportion of Tier 1 epilepsy gene publications by pathway



Macnee et al., 2023

Impact of Minor Alleles

Pharmacogenomics

HLA-B* 1502

- Chung WH, et al., *Nature*, 2004 - strong association in Han Chinese between HLA-B*1502, and Stevens-Johnson syndrome induced by carbamazepine
- Tangamornsuksan W, et al. (2013) – meta analysis; **OR ~80** in Han Chinese, Thais, and Malaysians (not detected in individuals of white or Japanese ethnicity/ race)
- This may also be associated with phenytoin (Cheung YK, et al. *Epilepsia,* 2013) and lamotrigine (Zeng T, et al., 2015)
- HLA-A*3101 allele (2-5% prevalence in Northern Europeans) associated with carbamazepine-induced hypersensitivity (risk increased from 5% to 26*) (McCormack M, et al., *NEJM,* 2011)

HLA-B*1502 allele frequency

Continent	Population/ethnicity	Allele frequency (%)	n
North America	Asian	5.1	396
	African	0.2	251
	European	0	287
	Hispanic	0	240
	Native American	0	235
Asia	Korean	0.5	200
	Han Chinese	10.2	572
	Singapore	11.6	86
	Malay	8.4	101
	Thai	6.1	99
	Filipino	5.3	94
	India Mumbai Marathas	1	72
	India North Hindi	2	91
	India Khandesh Pawra	6	50

[102]Middleton D: Allele Frequencies in Worldwide Populations www.allelefrequencies.net

[103]International Histocompatibility Working Group www.ihwg.org

FDA

- FDA ALERT [12/12/2007]: Dangerous or even fatal skin reactions (Stevens Johnson syndrome and toxic epidermal necrolysis), that can be caused by carbamazepine therapy, are significantly more common in patients with a particular human leukocyte antigen (HLA) allele, HLA-B*1502. This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians. Genetic tests for HLA-B*1502 are already available. **Patients with ancestry from areas in which HLA-B*1502 is present should be screened for the HLA-B*1502 allele before starting treatment with carbamazepine.** If they test positive, carbamazepine should not be started unless the expected benefit clearly outweighs the increased risk of serious skin reactions. Patients who have been taking carbamazepine for more than a few months without developing skin reactions are at low risk of these events ever developing from carbamazepine. This is true for patients of any ethnicity or genotype, including patients positive for HLA-B*1502. This new safety information will be reflected in updated product labeling

Review article

Pharmacogenomics in epilepsy

Simona Balestrini [a,b], Sanjay M. Sisodiya [a,*]

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Table 1
Influence of genetic factors on response and adverse reactions to AEDs through various mediators: summary of existing findings.

Response		
Mediator	Genetic factor	Effect [references]
Pharmacokinetics and pharmacodynamics	Variation in *CYP2C9* gene	Risk of developing concentration-dependent neurotoxicity from phenytoin [12,13]- established evidence
	Variation in *CYP2C19* gene	Association with the serum concentration of N-desmethylclobazam and with its clinical efficacy, indicating a gene-dose effect [17–21]
	Variation in *CYP2C19* gene	Ethnic differences in the tolerability profile of phenobarbital [22]
	UGT1A1 variants	Altered clearance of lamotrigine [25]
	Variation in *CYP2C19* gene	Risk of adverse reactions from zonisamide [28]
	Variation in *SCN1A*, *ABCC2*, *UGT2B7* genes	Association with oxcarbazepine maintenance doses [36]
	Variation in *CYP1A1* gene	Association with response to first-line antiepileptic drugs in Indian women [37,38]
	ABCB1 gene (encoding P-glycoprotein, P-gp, multidrug transporter) variants	Drug-resistant epilepsy [40–45]
	Variation in genes coding for AED targets	No significant association with drug response [49–53]
Adverse reactions	*HLA-B*15:02*	Stevens-Johnson syndrome and toxic epidermal necrolysis induced by carbamazepine and other aromatic AEDs in patients from Han Chinese and other South Asian ethnic groups [165–170]- established evidence
	*HLA-A*31:01*	Increased risk of carbamazepine-induced hypersensitivity reactions in patients of European ancestry and in the Japanese population [172,173]- established evidence
	T1405 polymorphism of the *CPS1* gene	Increased risk of valproate-induced hyperammonaemia in Caucasian patients [176]
	Val16Ala polymorphism of the *SOD2* gene	Elevated serum level of γ-glutamyltransferase induced by valproate in Japanese patients [179]
	Polymorphic *LEPR* and *ANKK1* genes	Weight gain on valproate in Han Chinese patients [180]
	Variation in *CYP2C9* and *CYP2A6* genes	Risk of toxicity from valproate [181,182]

Copy Number Variants

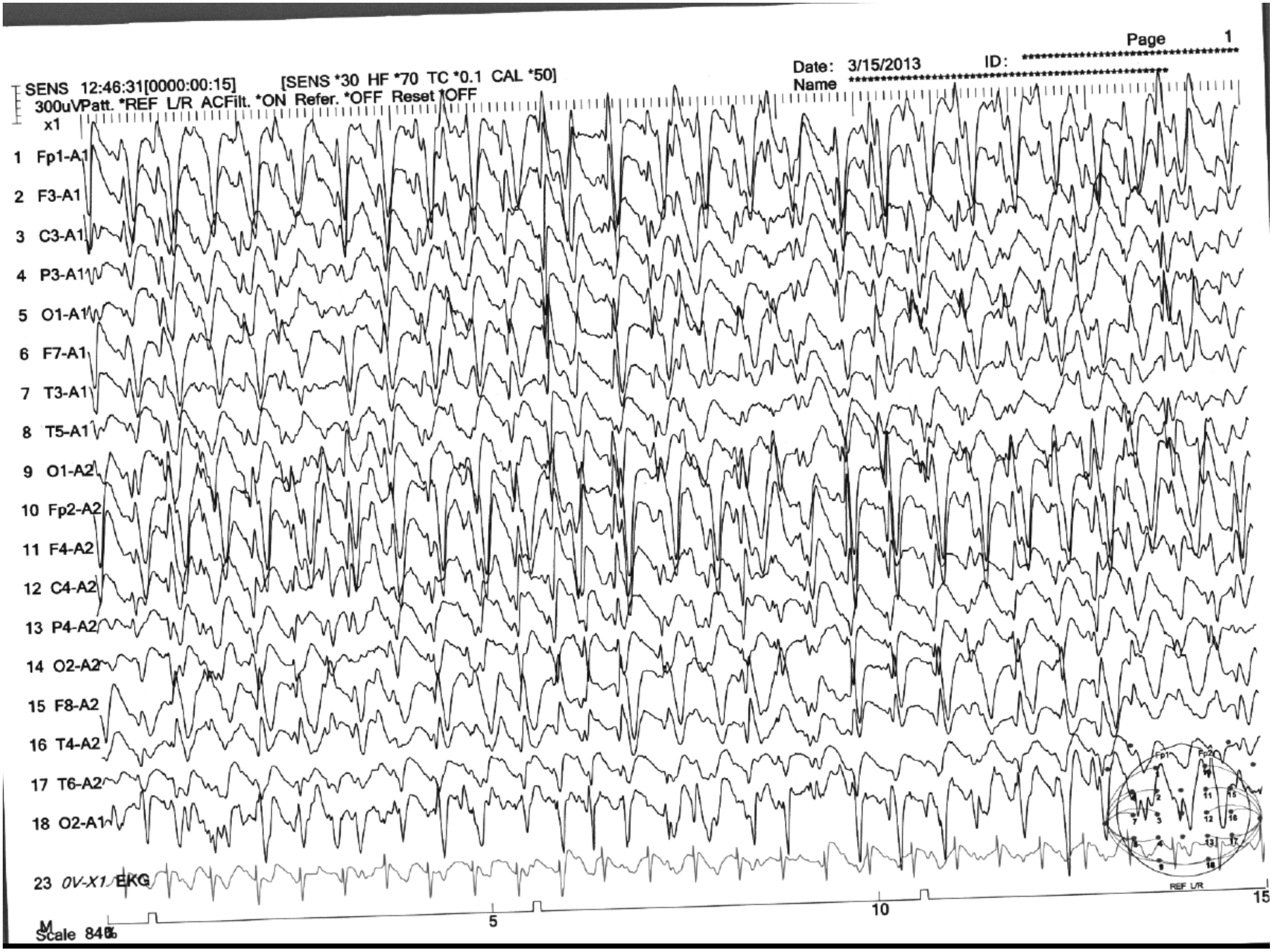
Chromosome Microarray

Copy Number Variants

- Criteria determining significance:
  - Size
  - Gene content
  - Presence or absence in control population
  - Inheritance
- Contribution to disease and phenotypic variability
  - Haploinsufficiency
  - Imprinting
  - Unmasking a recessive allelic mutation
  - Other background genomic variation

Copy Number Variants and Epilepsy

- Epileptic Encephalopathies – Mefford et al., 2011
  - Oligonucleotide array in 315 with EE
  - 25/315 (7.9%) had rare CNVs
  - > ½ clearly or likely pathogenic
- Infantile Spasms – Paciorkowski et al., 2011
  - Analyzed gene content of non-recurrent CNVs and deletion 1p36 in new and published IS subjects
  - Found gene content enriched for networks involved in ventral forebrain development, synaptic function, and GABAergic neurotransmission
- GGE ± ID – Mullen et al., 2013
  - Screened for recurrent microdeletions at 15q13.3, 15q11.2, and 16p13.11
  - Detected in 11/359 probands with genetic generalized epilepsy (GGE) and **6/60 with GGE and intellectual disability** (and another 13/60 rare CNVs [6 were also found in an unaffected parent])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[SENS *30 HF *70 TC *0.1 CAL *50]
300uVPatt. *REF L/R ACFilt. *ON Refer. *OFF Reset *OFF
x1
1 Fp1-A1
2 F3-A1
3 C3-A1
4 P3-A1
5 O1-A1
6 F7-A1
7 T3-A1
8 T5-A1
9 O1-A2
10 Fp2-A2
11 F4-A2
12 C4-A2
13 P4-A2
14 O2-A2
15 F8-A2
16 T4-A2
17 T6-A2
18 O2-A1
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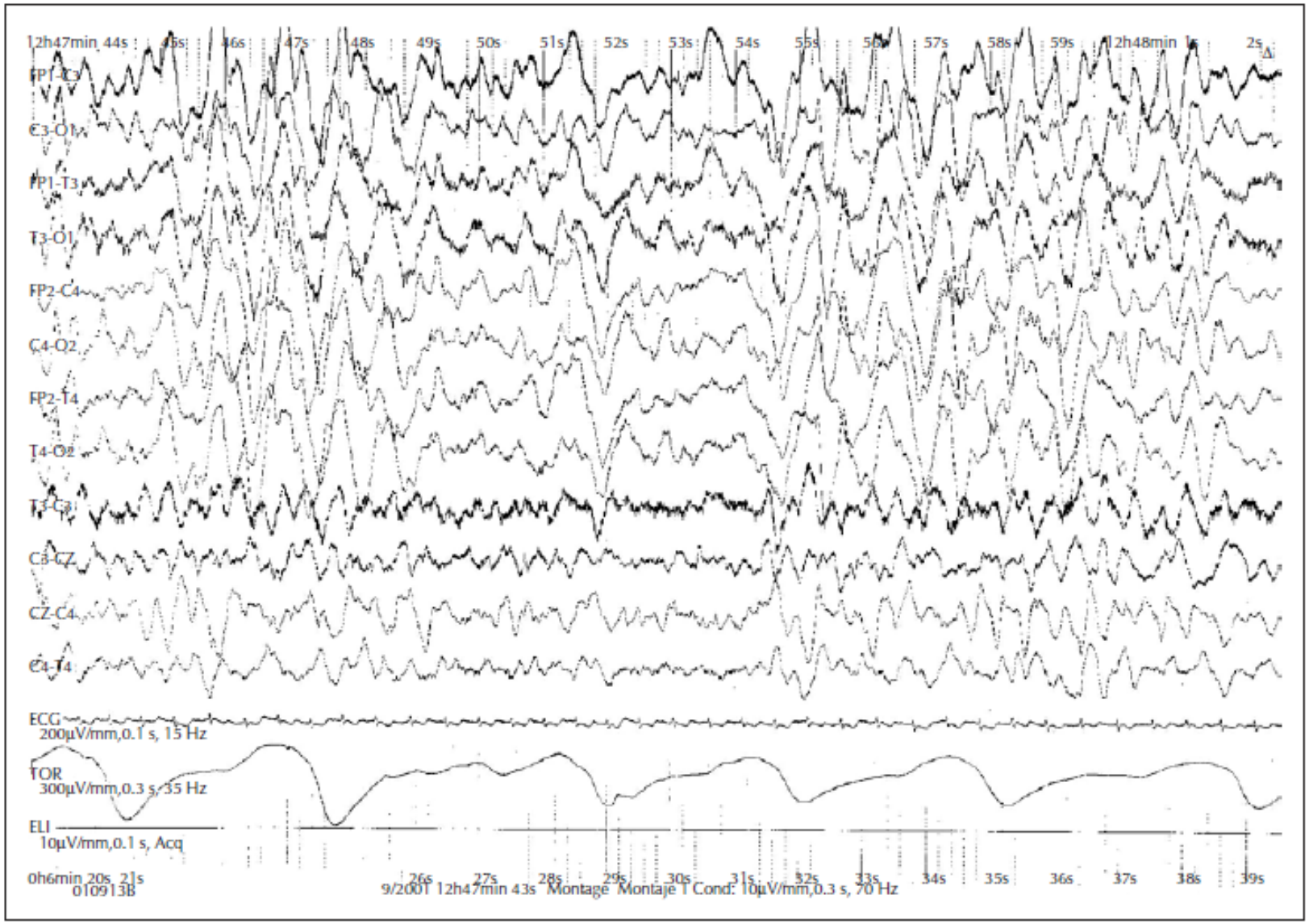


Figure 1. Typical EEG with high amplitude rhythmic 2-3/s activity in a 3-year-old boy with AS.

Laan LA, et al., 1999

Angelman Syndrome

- 1:12,000-20,000
- Newborns typically have a normal phenotype
- Developmental delays are first noted at around age 6 months, but many of unique features of AS do not manifest until > 1 year
- MRI or CT is usually normal, although mild cortical atrophy or dysmyelination may be observed
- *UBE3A* gene encodes ubiquitin-protein ligase – targets proteins for degradation (only maternally inherited copy is normally active in the brain due to paternal imprinting)

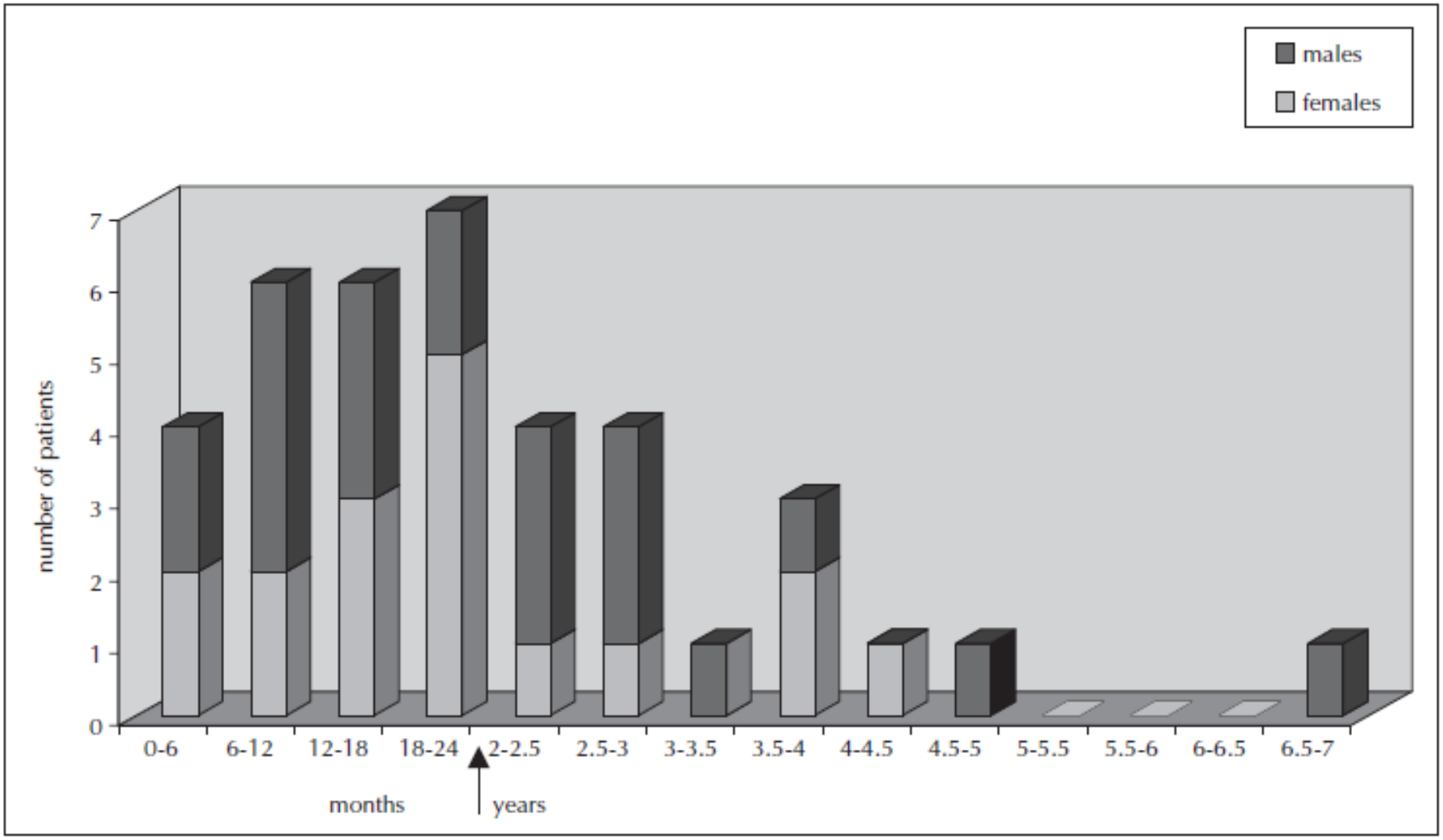
Table 1 Main clinical characteristics of AS

Consistent (100%)	Frequent (more than 80%)	Associated (20–80%)
Severe developmental delay Speech impairment, no or minimal use of words; receptive and non-verbal communication skills higher than verbal ones Movement or balance disorder, usually ataxia of gait and/or tremulous movement of limbs Behavioural uniqueness†: any combination of frequent laughter/smiling; apparent happy demeanor; easily excitable personality, often with hand flapping movements; hypermotoric behaviour; short attention span	Delayed, disproportionate growth in head circumference, usually resulting in microcephaly by age 2 Seizures, onset usually <3 years of age Characteristic EEG with large amplitude slow spike waves and triphasic waves	Flat occiput Occipital groove* Protruding tongue Tongue thrusting; suck/swallowing disorders Feeding problems during infancy Prognathia Wide mouth, widely spaced teeth Frequent drooling Excessive chewing/mouthing behaviours Strabismus Hypopigmented skin, light hair and eye colour (compared to family), seen only in deletion cases Hyperactive lower limb deep tendon reflexes Uplifted, flexed arm position especially during ambulation Increased sensitivity to heat Sleep disturbance Attraction to/fascination with water

Adapted from Williams CA, *et al*. Angelman syndrome: consensus for diagnostic criteria. *Am J Med Genet* 1995;**56**:237–8.
*Although emphasised particularly in Harry Angelman's first description, we have not found this to be a particularly useful sign.
†The characteristic behavioural phenotype has been shown to be perhaps the most useful diagnostic marker for AS.


A
B
C
D
E
F

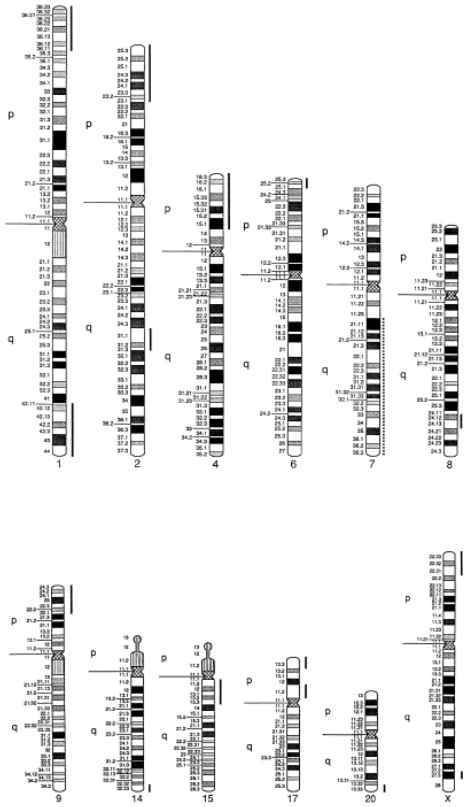
Table 1. Age at onset of epilepsy in Angelman syndrome (n=35).



Top chromosomal disorders implicated in epilepsy:

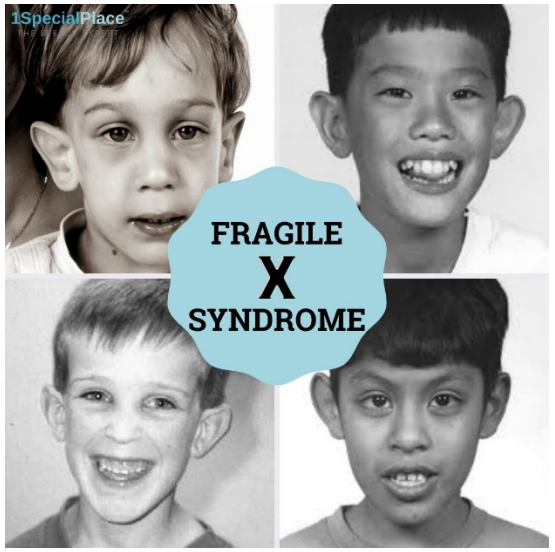
- dup15q
- Angelman (deletion 15q11-q13)
- deletion 1p36
- trisomy 21
- ring chromosome 14
- ring chromosome 20
- deletion 4p (Wolf-Hirschhorn)
- Miller-Dieker (deletion 17p13.3)
- deletion 1q (deletion 1qter->q42 or q43)
- deletion 2p (deletion 2p24->pter and deletion 2p23->p25)
- deletion 15q13.3
- deletion 16p13.11
- deletion 15q11.2
- deletion 18q
- tetrasomy 12p (Pallister-Killian)
- Klinefelter syndrome (XXY)
- Phelan McDermid, deletion 22q13.3

Chromosomal Abnormalities and Epilepsy: A Review for Clinicians and Gene Hunters



Epilepsia, Volume: 43, Issue: 2, Pages: 127-140, First published: 19 March 2002, DOI: (10.1046/j.1528-1157.2002.19498.x)

Fragile X Syndrome

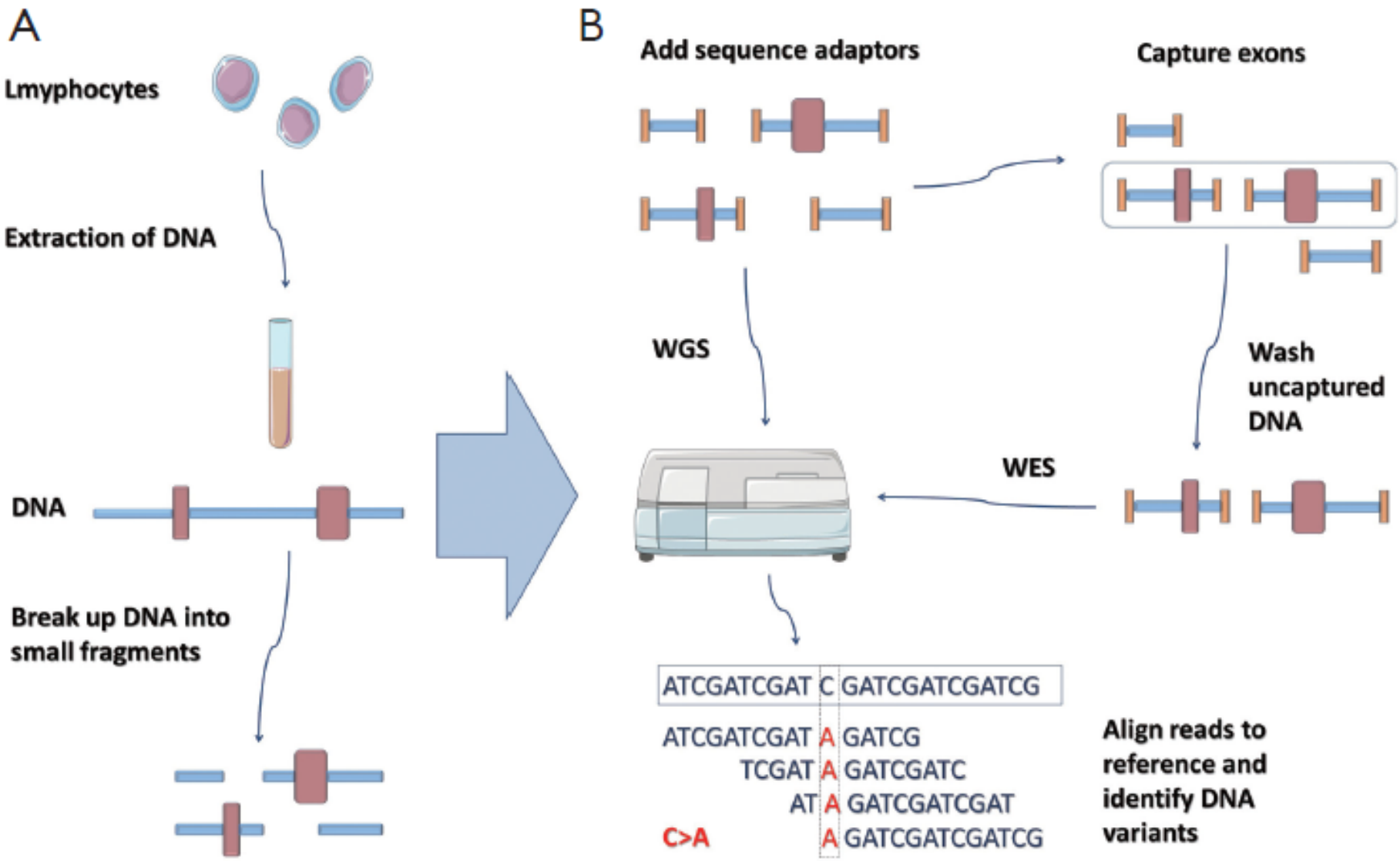


- 1/6000 males
- CGG expansion of FMR1 (>200; normal <50)
- Developmental delay/ ID
- Behavioral disorders
- ASD
- Dysmorphic features – long face, prominent forehead, large ears, prominent jaw (more obvious age but only in subset, not reliable), macroorchidism (post-pubertal)
- Medical problems – seizures, hypotonia, GERD, strabismus, sleep disorders, mitral valve prolapse and aortic root dilatation (adults)
- Heterozygous females are asymptomatic or have milder symptoms
- Others (pre-mutation)
  - Fragile X-associated tremor/ ataxia syndrome
  - Fragile X-associated primary ovarian insufficiency

Next Generation Sequencing

Gene panels

Whole exome sequencing



Jiang et al., 2014

Epilepsy Gene Panel – Children's National

- ADSL
- ALDH7A1
- AMT
- ARHGEF9
- ARX
- ATP1A2
- ATP6AP2
- CACNB4
- CDKL5
- CHRNA2, 4, 7
- CHRNB2
- CLN3, 5, 6, 8
- CNTNAP2
- CSTB
- CTSD
- DNAJC5
- EFHC1
- EPM2A
- FOLR1
- FOXG1
- GABRA1
- GABRB3
- GABRG2
- GAMT
- GATM
- GCSH
- GLDC
- GOSR2
- GPHN
- GRIN2A/B
- KANSL1
- KCNJ10
- KCNQ2, 3
- KCTD7
- LGI1
- LIAS
- MAGI2
- MBD5
- MECP2
- MEF2C
- MFSD8
- MOCS1, 2
- NHLRC1
- NRXN1
- PCDH19
- PLCB1
- PNKP
- PNPO
- POLG
- PPT1
- PRICKLE1
- PRICKLE2
- PRRT2
- SCARB2
- SCN1A/B
- SCN2A
- SCN8A
- SCN9A
- SLC25A22
- SLC2A1
- SLC9A6
- SPTAN1
- SRPX2
- ST3GAL3
- STXBP1
- SUOX
- SYN1
- TBC1D24
- TCF4
- TPP1
- TSC1
- TSC2
- UBE3A
- ZEB2

Customized multigene panels in epilepsy: the best things come in small packages

Simona Pellacani[1] · Claudia Dosi[1] · Giulia Valvo[1] · Francesca Moro[2] · Serena Mero[2] · Federico Sicca[1,2] · Filippo Maria Santorelli[2]

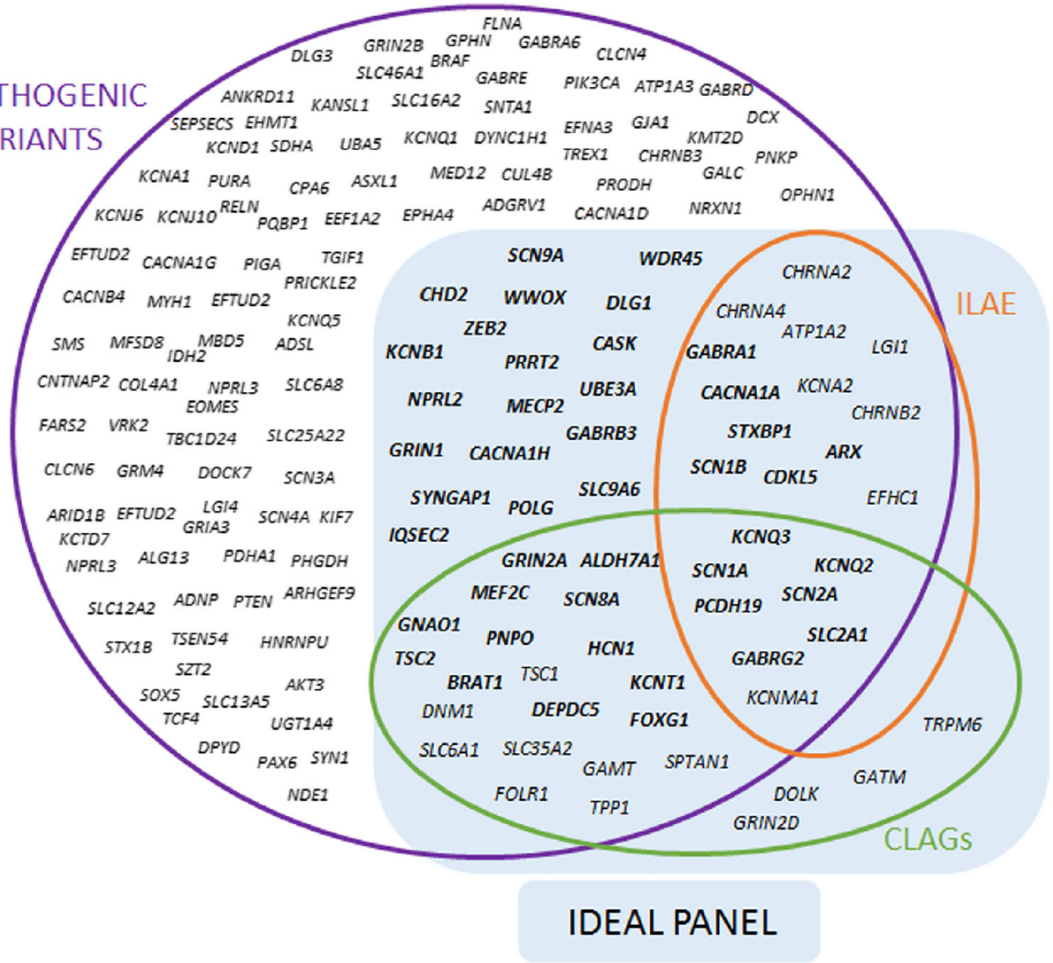


Fig. 4 Graph showing the composition of the "ideal" epilepsy panel. In bold the 45 genes harboring at least five pathogenic variants identified in our literature search (see text for details)

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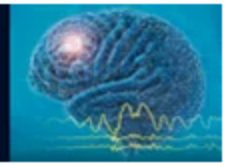


RESEARCH ARTICLE | Open Access

Genes4Epilepsy: An epilepsy gene resource

Karen L. Oliver, Ingrid E. Scheffer, Mark F. Bennett, Bronwyn E. Grinton, Melanie Bahlo, Samuel F. Berkovic

First published: 21 February 2023 | https://doi.org/10.1111/epi.17547 | Citations: 1

- Epilepsy clinical panels evaluated range from 144-511 genes
- Manual curation of all “epilepsy genes” yielded >900 monogenic etiologies (excluded limited or disputed evidence)
- **github.com/bahlolab/genes4epilepsy**

Interpretation (VUS ≠ mutation)

- Confirm with direct sequencing
- Known mutation/ known gene
- **Clinical Interpretation – epilepsy phenotype**
- Unknown mutation/ unknown gene
  - Population frequency – compare to SNP databases (1000 Genomes Project, NHLBI Exome Sequencing Project, ExAC browser, gnomAD, others)
  - Mutation type, comparative sequence analysis (conserved across species?)
  - Protein function (PolyPhen scores, SIFT, others)
  - Gene-specific tolerance to mutation
  - Evaluate trios and inheritance pattern (e.g. recessive vs dominant)
  - Variant-phenotype databases (ClinVar, DECIPHER), genematcher, etc
  - Functional assays

Epilepsy Syndromes

- Neonatal/ Infancy:
  - benign familial neonatal epilepsy, benign neonatal epilepsy, early myoclonic epilepsy, early infantile epileptic encephalopathy, epilepsy of infancy with migrating focal seizures, West syndrome, benign myoclonic epilepsy in infancy, severe myoclonic epilepsy in infancy (Dravet), benign familial infantile convulsions, familial infantile convulsions and paroxysmal choreoathetosis
- Childhood:
  - febrile seizures, febrile seizures plus, astatic-myoclonic epilepsy of Doose, Lennox-Gastaut syndrome, benign epilepsy with centrotemporal spikes, childhood absence epilepsy, Panayiotopoulos syndrome, late onset childhood occipital epilepsy (Gastaut type), Landau Kleffner syndrome, epileptic encephalopathy with continuous spike wave of sleep
- Adolescence:
  - juvenile absence epilepsy, juvenile myoclonic epilepsy
- Other syndromes:
  - autosomal dominant nocturnal frontal lobe epilepsy, autosomal dominant epilepsy with auditory features, idiopathic (genetic) generalized epilepsy, progressive myoclonic epilepsy, familial focal epilepsy with variable foci, gelastic seizures with hypothalamic hamartoma, reflex epilepsy, Rasmussen syndrome,
- Focal or multifocal epilepsy (right/ left, frontal/ temporal/ parietal/ occipital, with/ without known structural lesion)

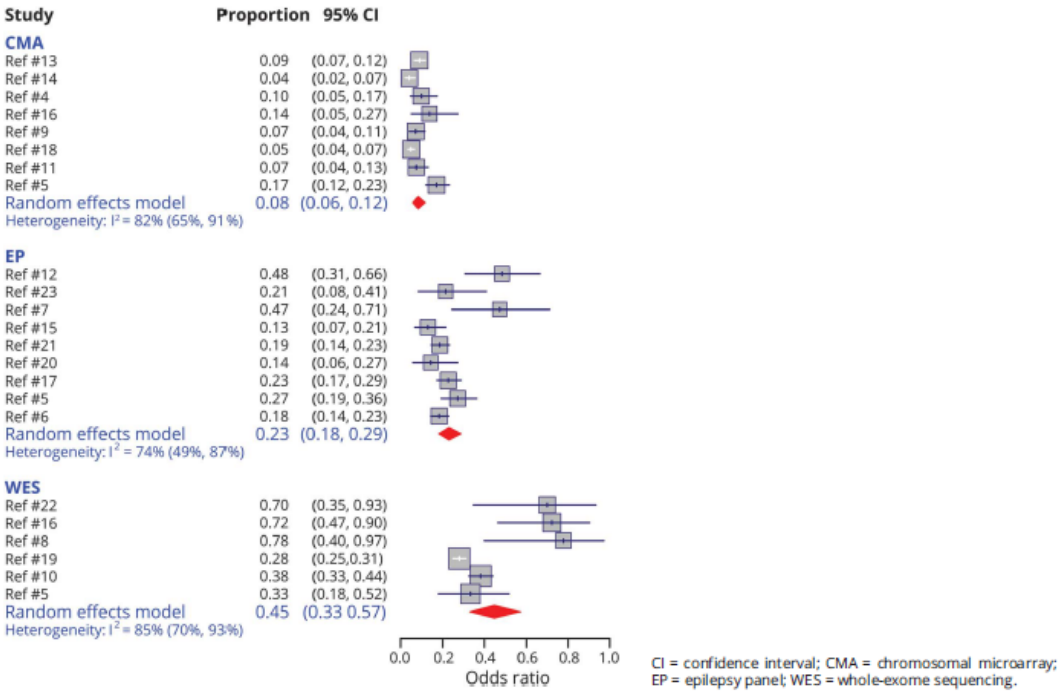
WES: Limitations

- Coverage in certain areas
- Structural variants (e.g. translocations and inversions)
- Triplet repeat disorders
- Intronic mutations
- Uniparental disomy
- Gene-gene interactions
- Epigenetic changes (e.g. methylation)
- Data processing
- Deletions and duplications
  - Deletions or duplications account for 8-27% of Dravet syndrome

Diagnostic yield of genetic tests in epilepsy

A meta-analysis and cost-effectiveness study

Figure 2 Meta-analysis of the diagnostic yield of the different genetic tests



CI = confidence interval; CMA = chromosomal microarray; EP = epilepsy panel; WES = whole-exome sequencing.

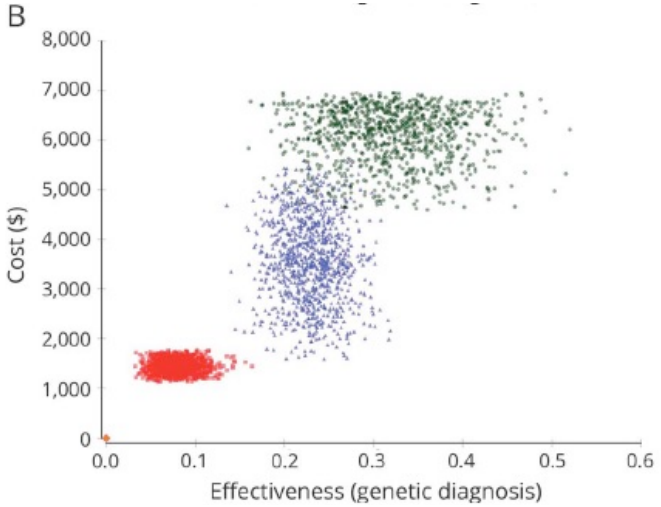


Figure 4 Comparison of individual tests: No genetic testing (orange diamond), CMA (red square), EP (blue triangle), and WES (green circle) adjusting for potential publication bias

Diagnostic Yield of Whole Genome Sequencing After Nondiagnostic Exome Sequencing or Gene Panel in Developmental and Epileptic Encephalopathies

Elizabeth Emma Palmer, MBBS, PhD, Rani Sachdev, MBBS, Rebecca Macintosh, GradDipGC, Uirá Souto Melo, PhD, Stefan Mundlos, MD, PhD, Sarah Righetti, MSc, Tejaswi Kandula, MBBS, PhD, Andre E. Minoche, PhD, Clare Puttick, BSc, Velimir Gayevskiy, PhD, Luke Hesson, PhD, Senel Idrisoglu, BSc(Hons), Cheryl Shoubridge, PhD, Monica Hong Ngoc Thai, BLabMed, Ryan L. Davis, PhD, Alexander P. Drew, PhD, Hugo Sampaio, MD, Peter Ian Andrews, MBBS, FRACP, John Lawson, MBBS, FRACP, Michael Cardamone, PhD, MBBS, FRACP, David Mowat, MBBS, Alison Colley, MBBS, FRACP, Sarah Kummerfeld, PhD, Marcel E. Dinger, PhD, Mark J. Cowley, PhD, Tony Roscioli, MBBS, PhD, Ann Bye, MD, and Edwin Kirk, MBBS, PhD

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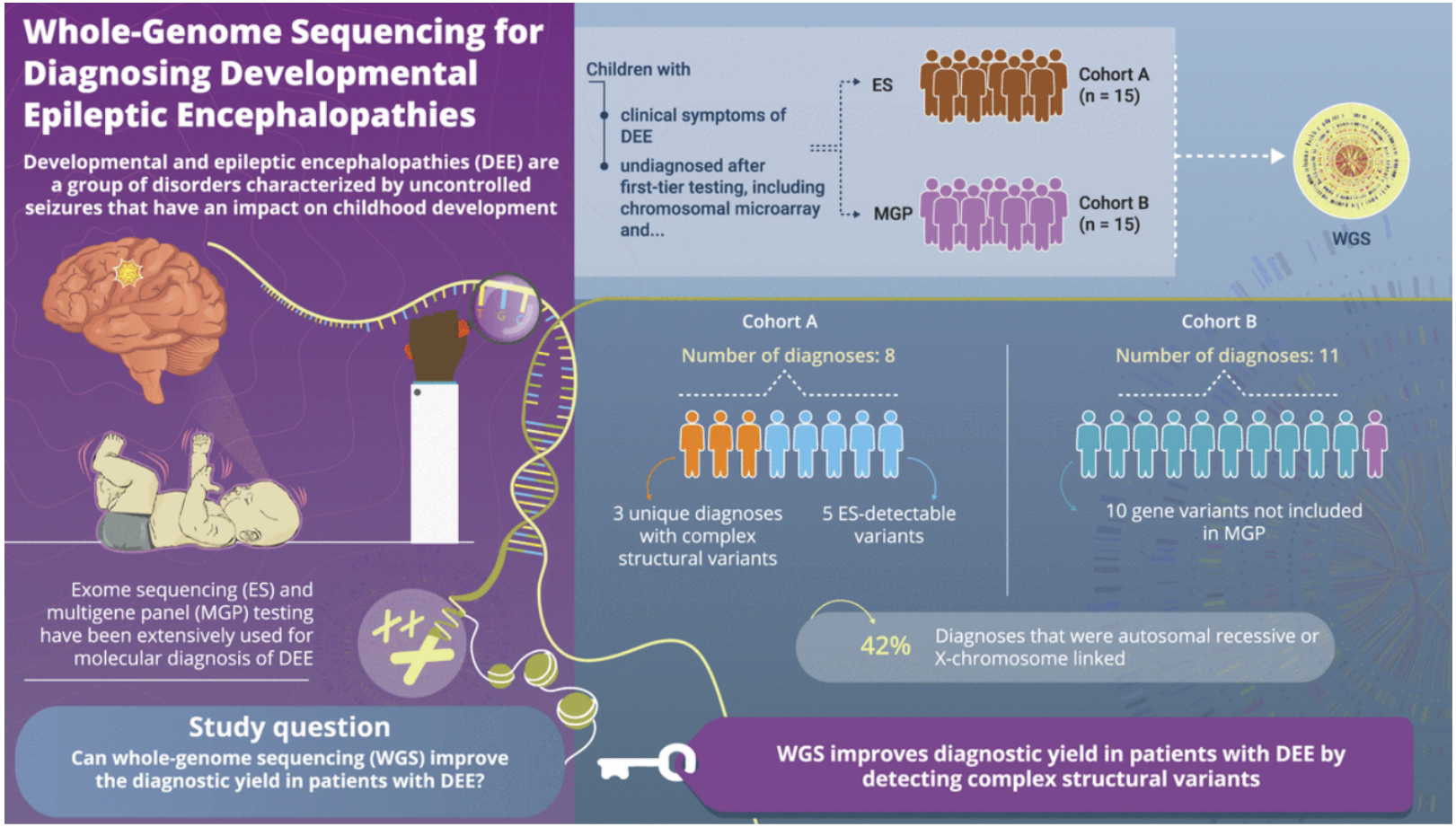
Neurology® 2021;96:e1770-e1782. doi:10.1212/WNL.0000000000011655



Specific Genes/ Conditions

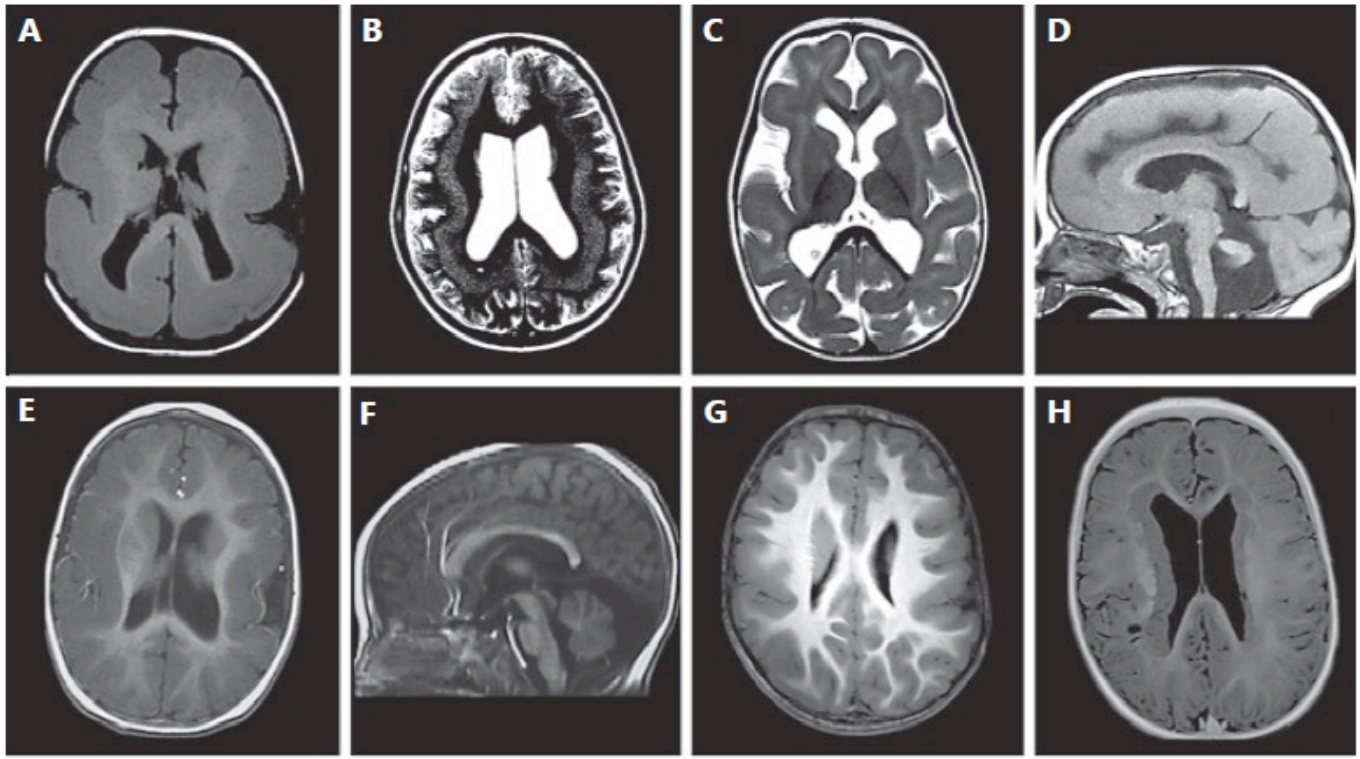
Inborn errors of metabolism

Malformations of Cortical Development

Infantile Spasms

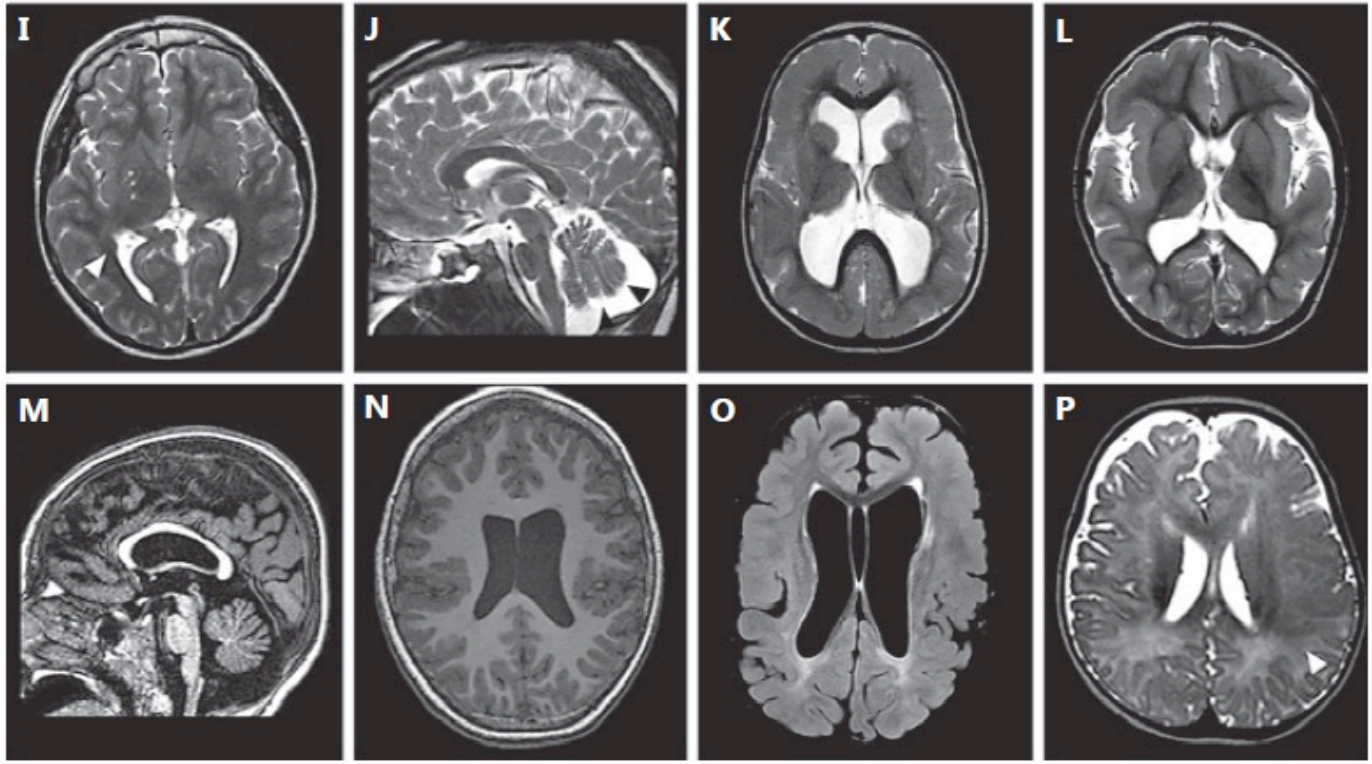
Monogenic Epilepsies

MCD



Mol Syndromol 2016;7:220–233
DOI: 10.1159/000448639

Fig. 1. Brain MRI of patients with different malformations of the cerebral cortex. **A** T1-weighted axial section. Posterior to anterior pachygyria in a boy with *LIS1* mutation. **B** T2-weighted axial section. Diffuse SBH in a girl with *DCX* mutation. **C**, **D** T2-weighted axial section and T1-weighted sagittal section. Lissencephaly and cerebellar hypoplasia in a girl with *RELN* mutation. **E**, **F** T1-weighted axial section and T1-weighted sagittal section. Thickened cortex with simplified gyral pattern and cerebellar hypoplasia in a girl with *TUBA1A* mutation. **G** T1-weighted axial section. Diffuse simplified gyral pattern with prominent thickening and infolding of the sylvian fissures in a boy with *TUBB2B* mutation. **H** T1-weighted axial section. Typical, classical bilateral PNH in a girl with an *FLNA* mutation. Bilateral nodules of subependymal heterotopia are contiguous and rather symmetric, extensively lining the ventricular walls.



I, J T2-weighted axial section showing mild colpocephaly with unilateral PNH (white arrowhead) and T2-weighted sagittal section through the midline, showing cerebellar vermis hypoplasia (black arrowhead) with mega cisterna magna in a patient carrying a deletion in the 6q27 chromosomal region. **K** T2-weighted axial section. Bilateral frontoparietal polymicrogyria in a boy with *GPR56* mutation. **L, M** T2-weighted axial section and T1-weighted coronal section. Pachygyria and perisylvian polymicrogyria in a girl with *DYNC1H1* mutation. **N** Axial T1-weighted section in a patient with a mosaic *PIK3R2* mutation. **O, P** T1-weighted and T2-weighted axial images form patients carrying mosaic mutations in the *MTOR* gene with different percentages of mosaicism [**O**: p.Thr1977Ile, 20% of mosaicism in blood, **P**: p.Ser2215Phe, 5.5% of mosaicism in dysplastic brain tissue) showing bilateral cortical dysgyria (**O**) and focal cortical dysplasia (**P**, white arrowhead)].

MCD categories

- Lissencephaly
- Periventricular Nodular Heterotopia
- Polymicrogyria
- Megalencephaly-polymicrogyria, dysplastic megalencephaly, focal cortical dysplasias

Genetic and imaging findings associated with MCDs

MCD Type	Group	Associated Genes	Associated Pathways and etiology	Imaging Findings
Microcephaly	Group I	*MCPH1, CENPJ, CDK5RAP2, WDR62, NDE1, NDE1, ASPM, CDK5RAP2, TUBA1A, TUBB2B, TUBB3, TUBG1, LIS1, DCX, DYNC1H, KIF5C, NDE1*	Neurogenesis and cell replication, tubulin and microtubule-associated proteins (MAP)	Small head size, small cerebellum and pons and lissencephaly (with tubulin and MAP-associated genes)
Megalencephaly spectrum	Group I	*AKT3, PIK3CA,* and *PIK3R2*	mTOR	Focal (localized), hemispheric or diffuse cortical enlargement, cerebellum and deep gray nuclei also enlarged, gray/white boundary blurring
FCD type IIa	Group I	*MTOR, DEPDC5,*and *PIK3CA*	mTOR	Gray/white matter blurring with apparent cortical thickness
FCD type IIb	Group I	*MTOR, DEPDC5, NPRL3*	mTOR	Cortical/sulcal T2 hyperintensity may extend to ventricular surface (transmantle sign)
Tubulinopathies	Group II	*TUBA1A, TUBB2B, TUBB3, TUBG1, LIS1, DCX, DYNC1H, KIF5C, NDE1*	Microtubule structure and function	Microcephaly, lissencephaly, fused basal ganglia (BG), cortical dysgyria, callosal abnormalities, asymmetric brainstem and small cerebellar vermis
Variant lissencephalies	Group II	*ARX, DCX, RELN* and *VLDR*	Reelin	**ARX** -Lissencephaly, callosal abnormalities, dysmorphic BG, hydrancephaly **Reelin** – lissencephaly in anterior-posterior gradient, cortical thicknening, small cerebellum and vermis
Gray matter heterotopia	Group II	*FLNA* and *ARFGEF2*	Neuroependyma/neuroepitheliium	Normal gray matter in abnormal locations
Cobblestone malformations	Group II	*GPR56, LAMB1, LAMB2, LAMC3* and *SRD5A3*	Dystroglycanopathies affecting pial limiting membrane	Lissencephaly/pachygyria or polymicrogyria (PMG), possible cerebellar involvement
Polymicrogyria (PMG)	Group III	1p36.3 and 22q11.2 mutations, mTOR genes	Etiology can be from prenatal ischemic, teratogenic or infectious brain injury	Perisylvian bilateral PMG (most common), associated with schizencephaly

Case 3

- 15 month old boy with a history of febrile status epilepticus and subsequent unprovoked hemiclonic seizures presents for a second opinion. He was started on oxcarbazepine initially and the dose has been increased, but seizures have been gradually worsening, now with frequent myoclonic jerks.

Question 3:

- For case 3, what is the most appropriate next medication?
  - Valproic acid
  - Lamotrigine
  - Phenobarbital
  - Lacosamide

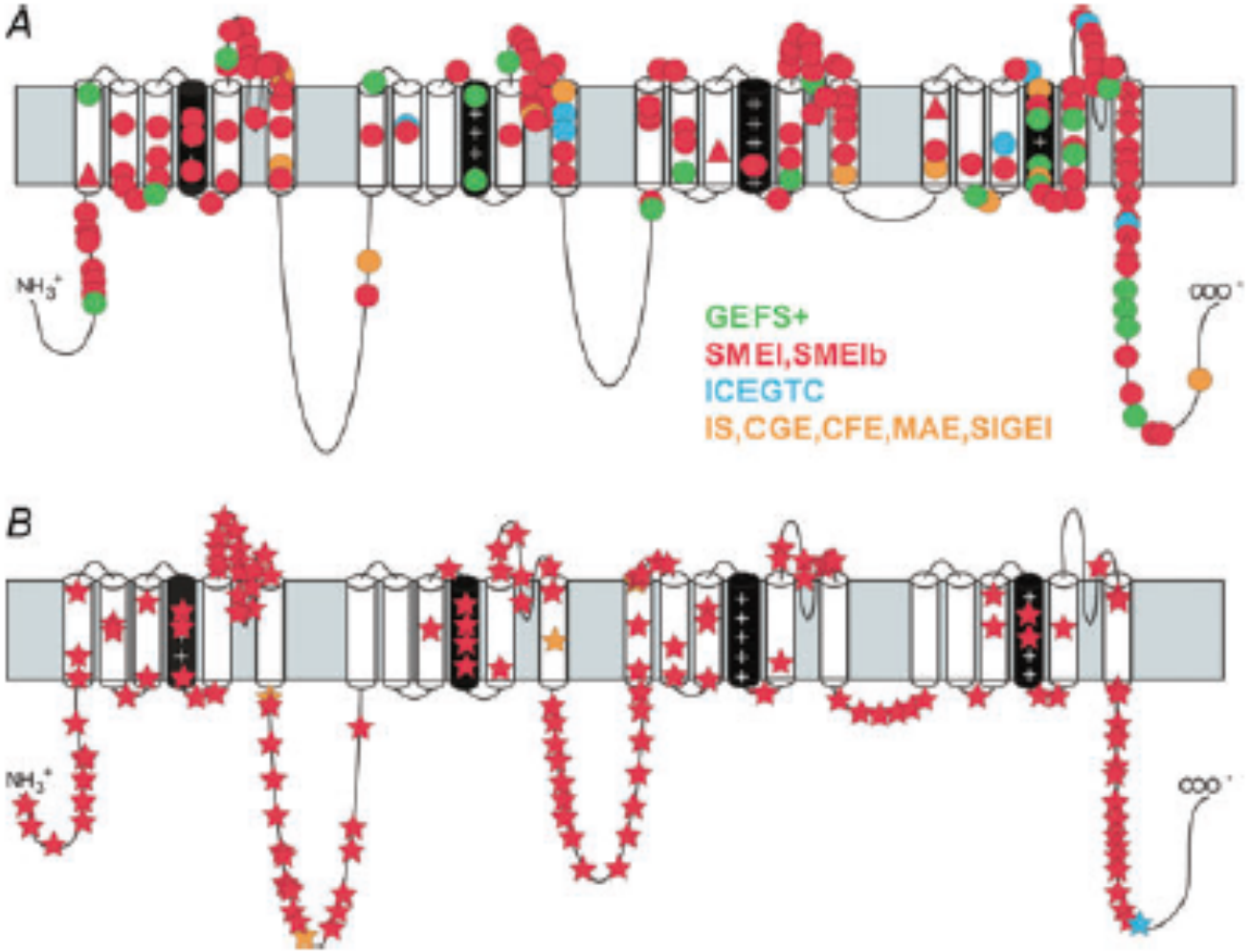


Figure 1. Mutations in $Na_V1.1$ channel patients with epilepsy

A, missense mutations (circles) and in-frame deletions (triangles). *B*, truncation mutations (stars). The clinical type of epilepsy is indicated by colour: GEFS+, generalized epilepsy with febrile seizures plus; SMEI, severe myoclonic epilepsy of infancy; SMEIb, borderline SMEI; ICEGTC, idiopathic childhood epilepsy with generalized tonic–clonic seizures; IS, infantile spasms; CGE, cryptogenic generalized epilepsy; CFE, cryptogenic focal epilepsy; MAE, myoclonic astatic epilepsy; SIGEI, severe idiopathic generalized epilepsy of infancy. Courtesy of M. Meisler and J. Kearney (Catterall *et al.* 2008).

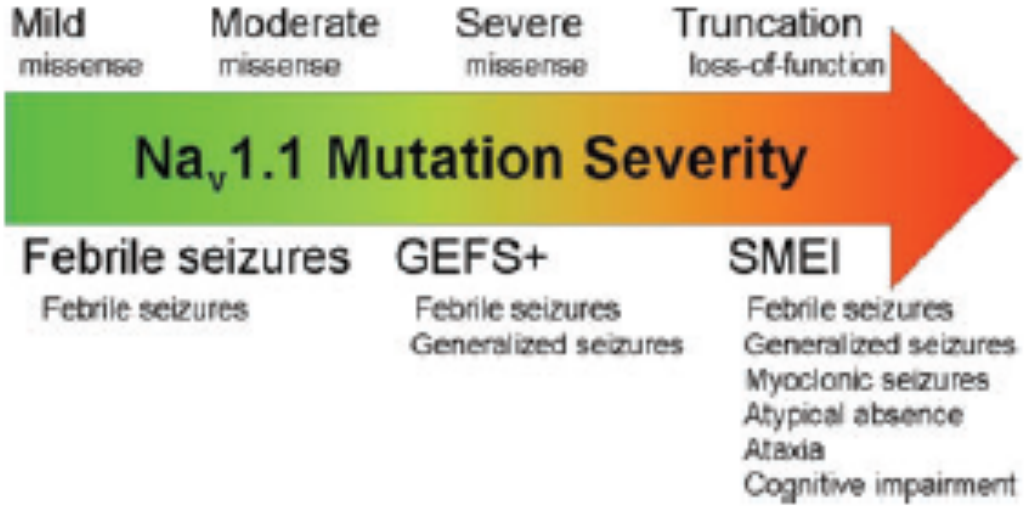


Figure 3. The unified loss-of-function hypothesis for Na$_V$1.1 genetic epilepsies

Increasing severity of loss-of-function mutations of Na$_V$1.1 channels, noted above the arrow, causes progressively more severe epilepsy syndromes from familial febrile seizures to GEFS+ and finally SMEI, noted below the arrow. Major symptoms of each syndrome are also listed.

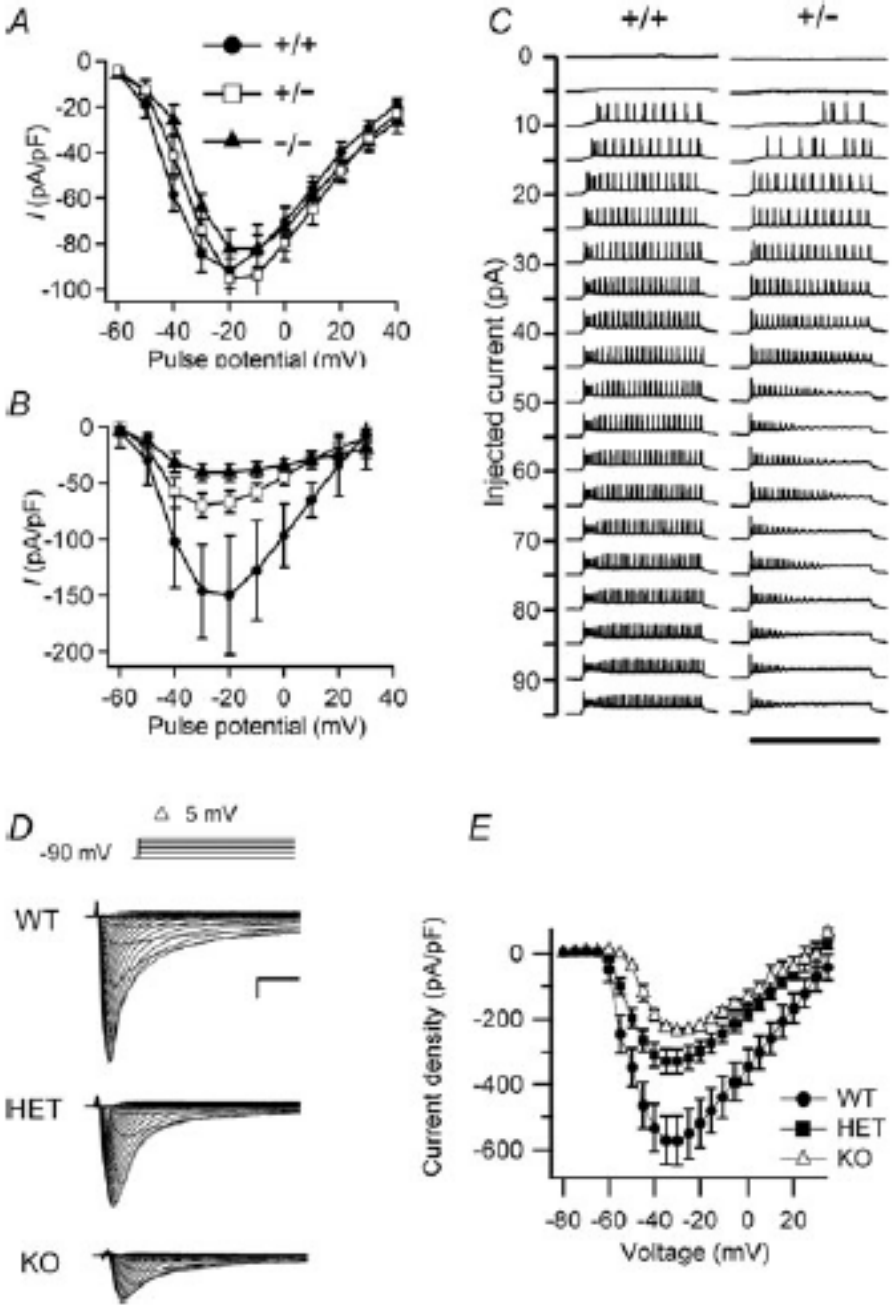
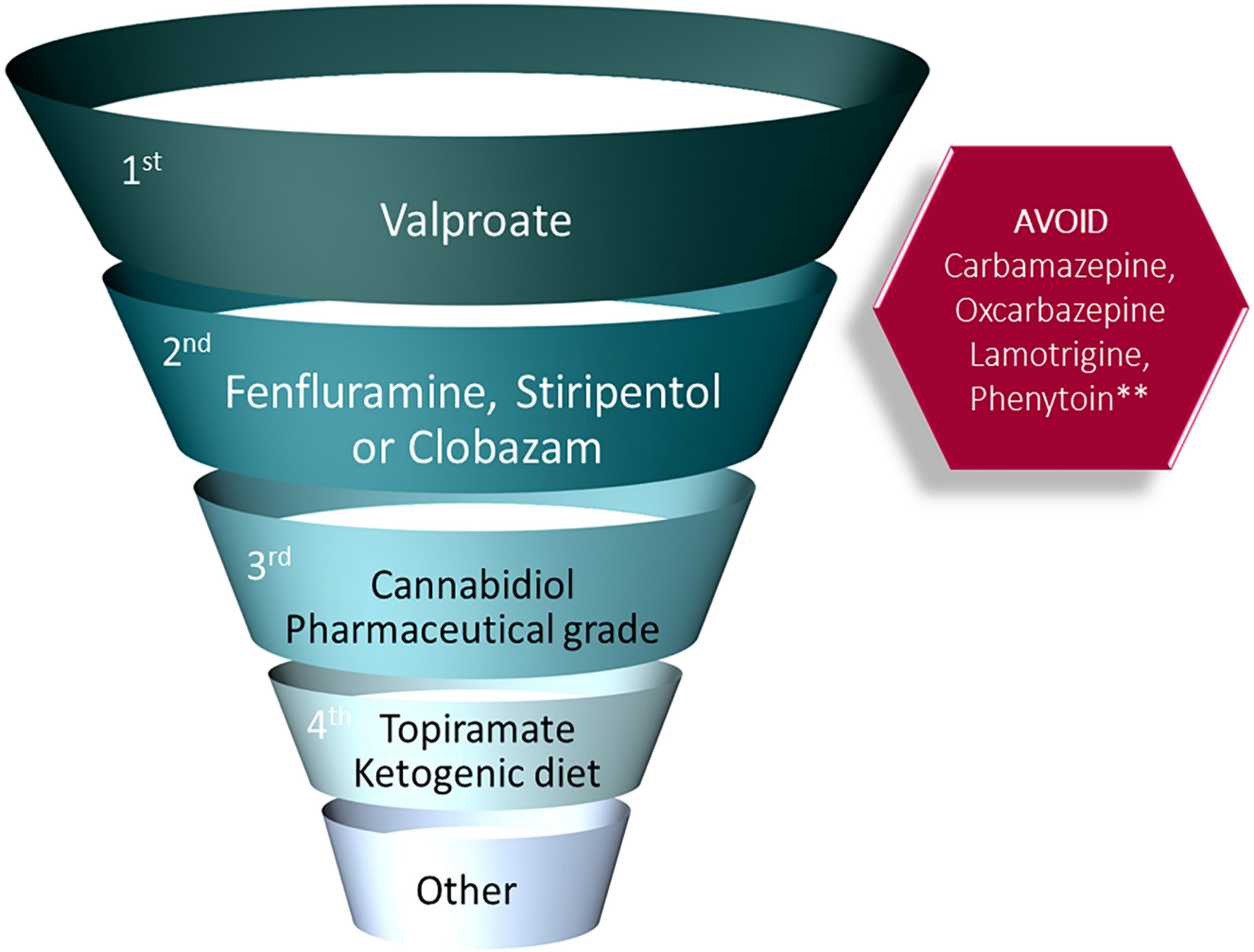


Figure 2. Sodium currents from hippocampal neurons and cerebellar Purkinje cells in wild-type, heterozygous and null $Na_V1.1$ mice

A and *B*, current–voltage relationships of whole-cell sodium currents from hippocampal pyramidal (*A*) and bipolar inhibitory neurons (*B*) for wild-type (circle), heterozygous (square) and homozygous (triangle) mice (Yu *et al.* 2006). *C*, action potential traces recorded from wild-type (+/+) and heterozygous (+/−) interneurons during application of 800-ms injections of depolarizing current in +10 pA increments from a holding potential of −80 mV (Kalume *et al.* 2007). *D*, sodium currents in cerebellar Purkinje neurons of WT, HET, and KO mice evoked with a series of 50 ms depolarizations from a holding potential of −90 mV to potentials ranging from −80 to + 30 mV in 5-mV increments. Inset, diagram of stimulus protocol. Scale bars: 1 ms, 2 nA. *E*, current–voltage relationships for WT (filled circles), HET (filled squares) and KO (open triangles) mice.



Epilepsia, Volume: 63, Issue: 7, Pages: 1761-1777, First published: 01 May 2022, DOI: (10.1111/epi.17274)

Status Epilepticus and SCN1A

- Screened for SCN1A mutations and deletions in 71 children age 1 month – 16 years with status epilepticus
- 12 were detected, including 10 children with clinical Dravet syndrome and 2 with generalized epilepsy with febrile seizures plus (GEFS+)
- Among 26 children aged **≤ 18 months** at initial episode of status epilepticus, risk of SCN1A mutation was significantly increased for patients with **≥ 2 episodes** (56.3%), as compared with those who had only one episode (0.0%)

Le Gal, *Epilepsy Res.,* 2014

Malignant migrating partial seizures in infancy/ EIMFS

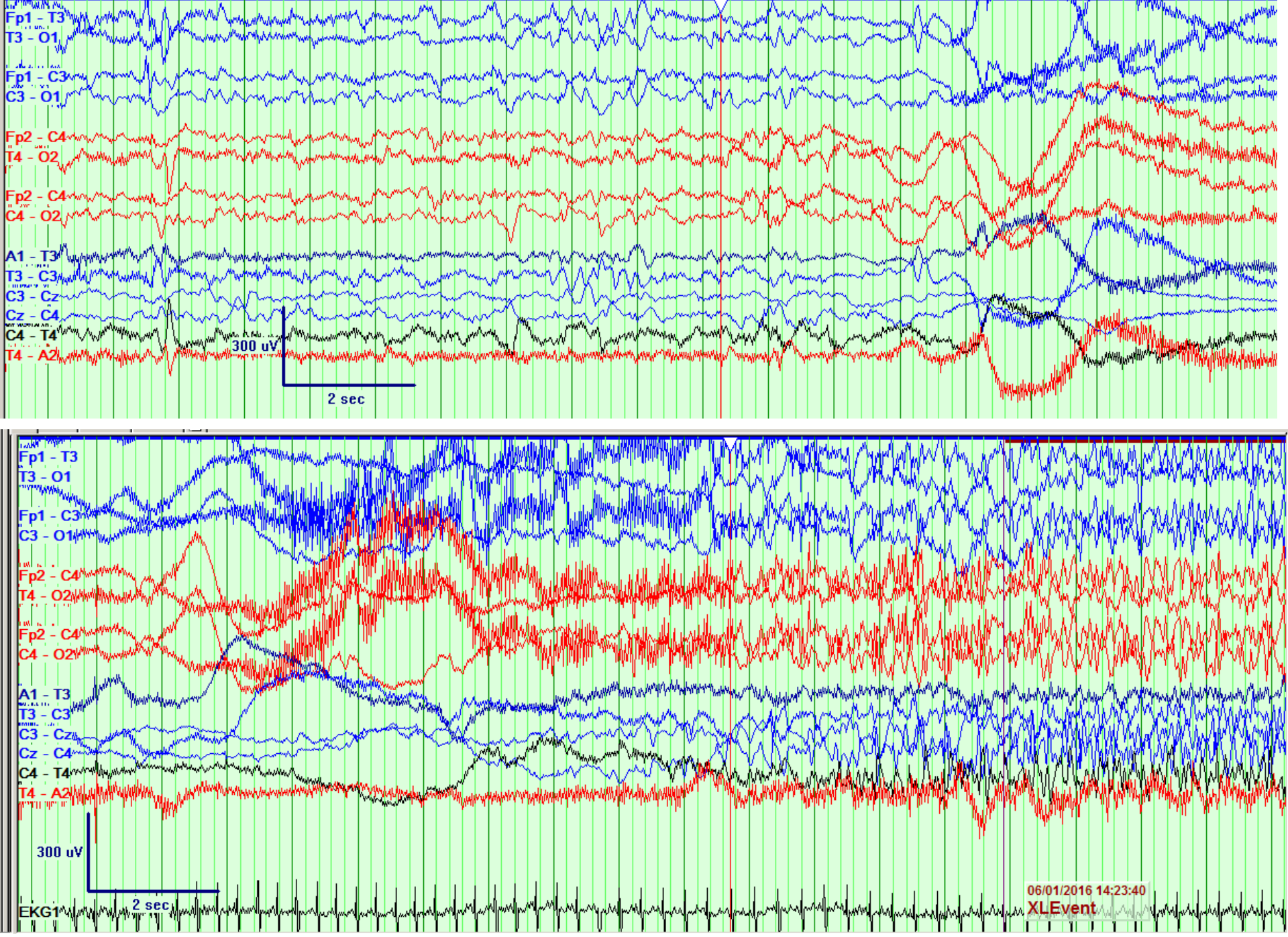
- Extremely rare and refractory form of epilepsy with intractable focal seizures
- Just over approximately 100 cases reported in the literature
- Vast majority have regression with severe developmental delay and microcephaly, in addition to severe and intractable seizures
- Significant risk for mortality in infancy and early childhood
- *KCNT1* (Barcia et al, 2012 in about ½), *SCN1A, SCN2A, SCN8A, TBC1D24, PNPO, KCNQ2, KCNQ3, STXBP1,PRRT2, etc*

KCNT1

- Activating mutations have been identified in ADNFLE and EIMFS
- In the early onset epileptic encephalopathies, it is largely restricted to EIMFS (Ohba C, et al. Epilepsia, 2015)
- *KCNT1* encodes a weakly voltage dependent and intracellular sodium activated potassium channel
- Quinidine
  - Mikati MA, et al. *Ann Neurol* 2015 – treated one patient with EIMFS (improved) and one with ADNFLE (not improved)
  - Milligan CJ, et al. *Ann Neurol* 2014 – quinidine significantly reduces gain of function in all mutations studied
  - However, this has not been substantiated by additional study

Case 4

- 4 week old baby presents with increased seizures manifested by focal jerking on either side of the body and/or apnea
- History – born full term via normal pregnancy and delivery; started having seizures at 1 week of life that improved some with levetiracetam
- Normal development and exam in between seizures


Fp1 - T3
T3 - O1
Fp1 - C3
C3 - O1
Fp2 - C4
T4 - O2
Fp2 - C4
C4 - O2
A1 - T3
T3 - C3
C3 - Cz
Cz - C4
C4 - T4
T4 - A2
300 uV
2 sec
Fp1 - T3
T3 - O1
Fp1 - C3
C3 - O1
Fp2 - C4
T4 - O2
Fp2 - C4
C4 - O2
A1 - T3
T3 - C3
C3 - Cz
Cz - C4
C4 - T4
T4 - A2
300 uV
2 sec
EKG1
06/01/2016 14:23:40
XLEvent

Question 4:

- What is the most appropriate diagnostic test for the patient described?
  - Chromosome microarray
  - Sequencing of *SCN1A*
  - Sequencing of *KCNQ2*
  - Sequencing of *KCNT1*
  - Pyridoxine challenge

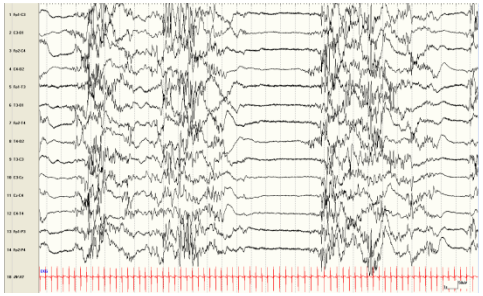
Benign Familial Neonatal Epilepsy

- “Fifth Day Fits”
- EEG background may be normal or abnormal
- Mutations in KCNQ2, or less commonly, KCNQ3
  - AD mutations, result in small reduction in current and less hyperpolarization
- Seizures - clonic, tonic, apneas, orofacial automatisms
- Benign idiopathic neonatal seizures
  - Almost always clonic seizures, mostly partial ± apnea

J Roger *et al.,* Epileptic Syndromes in Infancy, Childhood, and Adolescence

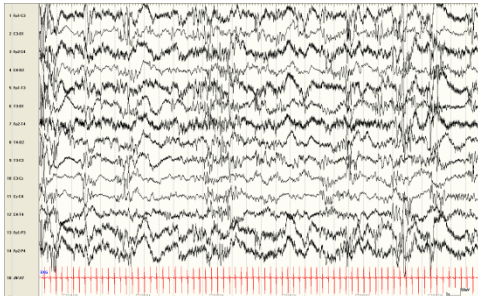
A

DOL6

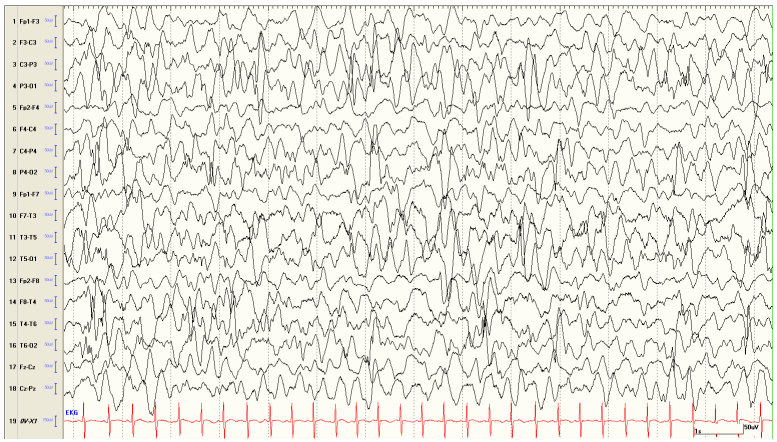


B

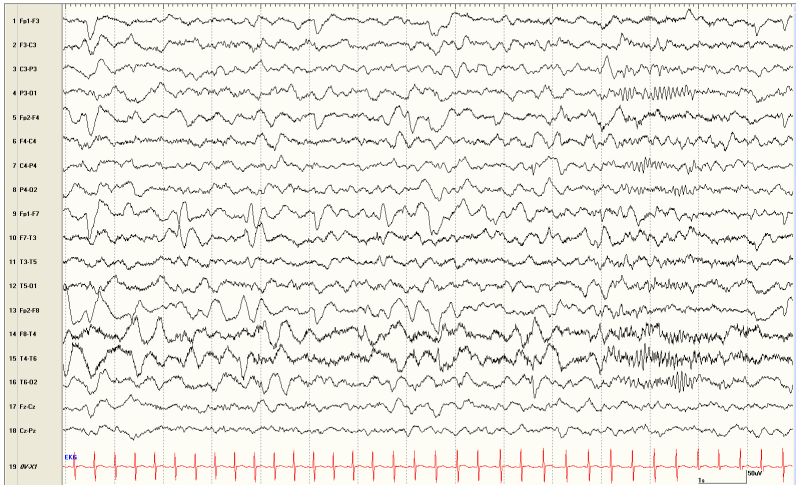
DOL6



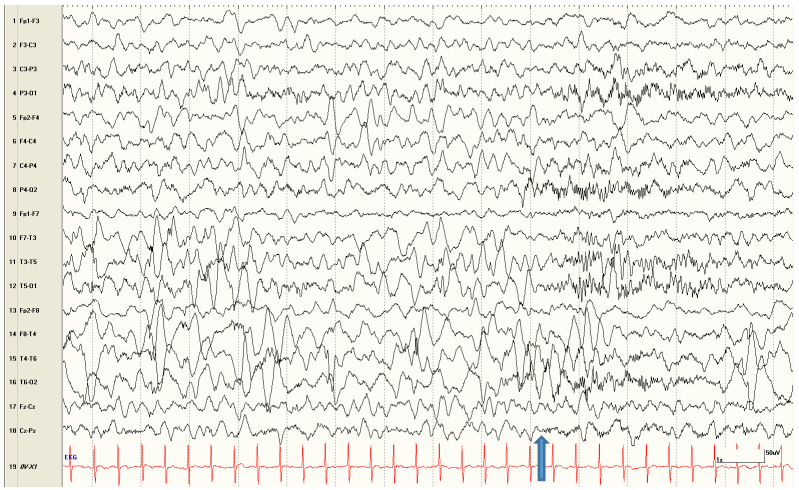
C 5mo (levetiracetam 70mg/kg, clobazam 0.8/kg, topiramate 5/kg



D 6 mo (ezogabine 23mg/kg, levetiracetam 70/kg, clobazam 0.8/kg)



E 7 mo (ezogabine 14 mg/kg, levetiracetam 70/kg, onfi 0.8/kg)



Unpublished, Courtesy of Dr. Tsuchida

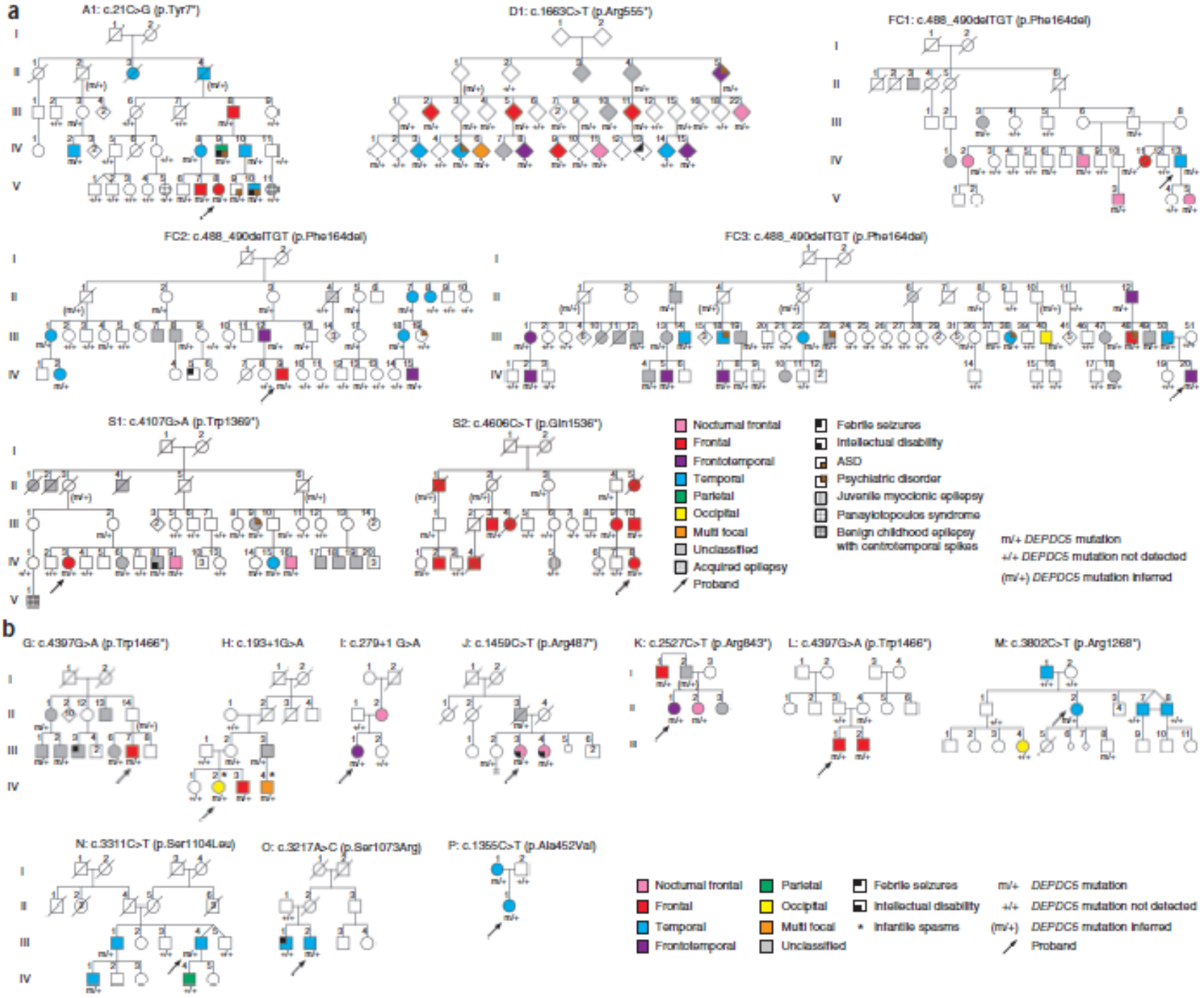
Case 5

- 14 year old boy with nonlesional focal epilepsy. Seizure onset was at age 11 manifested by head turn to the left with “figure of 4” posturing in arms with the left arm extended.
- Interictal and Ictal EEG shows bilateral frontal spike-wave discharges without clear laterality
- MRI brain and FDG-PET brain normal
- Family history notable for temporal lobe epilepsy in paternal grandmother and an ill-defined focal epilepsy in a paternal uncle

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

Leanne M Dibbens[1,2,23], Boukje de Vries[3,23], Simona Donatello[4], Sarah E Heron[1,2], Bree L Hodgson[1], Satyan Chintawar[4], Douglas E Crompton[5,6], James N Hughes[7], Susannah T Bellows[6], Karl Martin Klein[6,8], Petra M C Callenbach[9], Mark A Corbett[10], Alison E Gardner[10], Sara Kivity[11], Xenia Iona[1], Brigid M Regan[6], Claudia M Weller[3], Denis Crimmins[12], Terence J O'Brien[13], Rosa Guerrero-López[14], John C Mulley[7,15,16], Francois Dubeau[17], Laura Licchetta[18], Francesca Bisulli[18], Patrick Cossette[19], Paul O Thomas[7], Jozef Gecz[7,16], Jose Serratosa[14], Oebele F Brouwer, Frederick Andermann, Eva Andermann, Arn M J M van den Maagdenberg[3,20], Massimo Pandolfo[4], Samuel F Berkovic[6] & Ingrid E Scheffer[6,21,22]

NATURE GENETICS VOLUME 45 | NUMBER 5 | MAY 2013


a
A1: c.21C>G (p.Tyr7*)
D1: c.1663C>T (p.Arg555*)
FC1: c.488_490delTGT (p.Phe164del)
FC2: c.488_490delTGT (p.Phe164del)
FC3: c.488_490delTGT (p.Phe164del)
S1: c.4107G>A (p.Trp1369*)
S2: c.4606C>T (p.Gln1536*)
Nocturnal frontal
Frontal
Frontotemporal
Temporal
Parietal
Occipital
Multi focal
Unclassified
Acquired epilepsy
Proband
Febrile seizures
Intellectual disability
ASD
Psychiatric disorder
Juvenile myoclonic epilepsy
Panayiotopoulos syndrome
Benign childhood epilepsy with centrotemporal spikes
m/+ DEPDC5 mutation
+/+ DEPDC5 mutation not detected
(m/+) DEPDC5 mutation inferred
b
G: c.4397G>A (p.Trp1466*)
H: c.193+1G>A
I: c.279+1 G>A
J: c.1459C>T (p.Arg487*)
K: c.2527C>T (p.Arg843*)
L: c.4397G>A (p.Trp1466*)
M: c.3802C>T (p.Arg1268*)
N: c.3311C>T (p.Ser1104Leu)
O: c.3217A>C (p.Ser1073Arg)
P: c.1355C>T (p.Ala452Val)
Nocturnal frontal
Frontal
Temporal
Frontotemporal
Parietal
Occipital
Multi focal
Unclassified
Febrile seizures
Intellectual disability
* Infantile spasms
m/+ DEPDC5 mutation
+/+ DEPDC5 mutation not detected
(m/+) DEPDC5 mutation inferred
Proband

Question 5

- A 10 year old boy presents for a consult due to worsening generalized tonic-clonic seizures. Examination reveals mild dysmorphic facies including large ears and a long face. Family history is notable for a mother with bipolar disorder, maternal grandmother with depression, and a maternal uncle with a learning disability. What is the most likely finding on genetic testing?
  - Missense mutation in *SCN2A*
  - 1.2 MB deletion of chromosome 4p
  - 14 kB duplication of chromosome 1p
  - 250 CGG repeats in the *FMR1* gene
  - Nonsense mutation in *SCN1B*

Summary

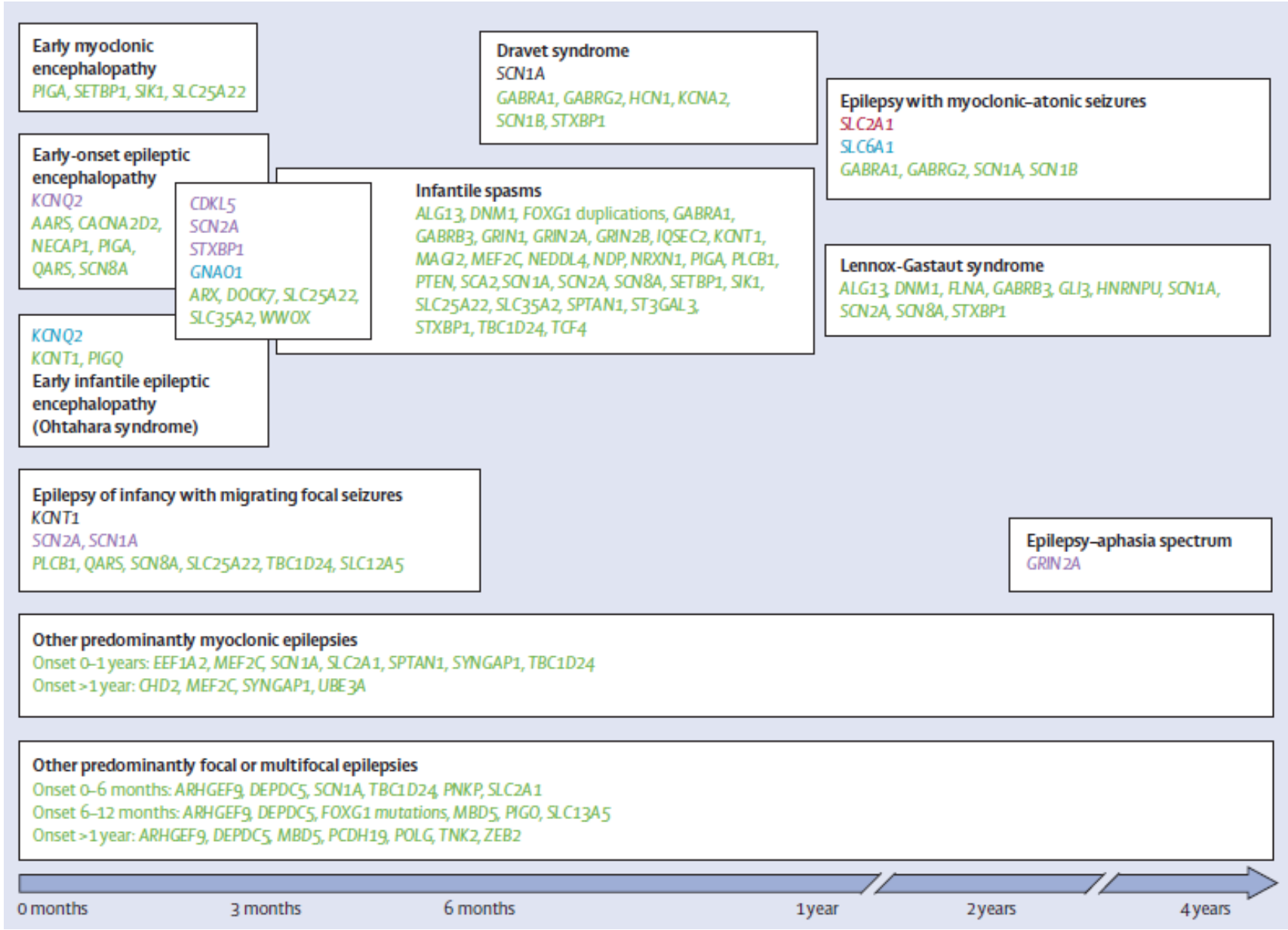
Epilepsy-Gene Associations

Genetic Epilepsies According to Age of Presentation

Precision Therapies

Select Epilepsy – Gene associations

- EIMFS – KCNT1 (nearly ½), SCN2A, SCN1A, others
- IS – STXBP1, SCN8A, SCN2A
- Ohtahara's – STXBP1, CDKL5, SCN2A
- FFEVF – DEPDC5
- Familial lateral temporal lobe epilepsy with auditory features – LGI1
- ADNFLE – CHRNA2, 4, 7; KCNT1
- Epilepsy-aphasia disorders – GRIN2A
- GEFS+ - SCN1A, SCN1B, SCN2A, GABRG2
- Dravet – SCN1A, PCDH19 (females)
- EPC – POLG1, MELAS
- Rett syndrome – MECP2
- For many epilepsy syndromes, there are multiple genetic causes
- Mutations in the same gene can result in vastly different epilepsy phenotypes


Early myoclonic encephalopathy
PIGA, SETBP1, SIK1, SLC25A22
Dravet syndrome
SCN1A
GABRA1, GABRG2, HCN1, KCNA2, SCN1B, STXBP1
Epilepsy with myoclonic–atonic seizures
SLC2A1
SLC6A1
GABRA1, GABRG2, SCN1A, SCN1B
Early-onset epileptic encephalopathy
KCNQ2
AARS, CACNA2D2, NECAP1, PIGA, QARS, SCN8A
CDKL5
SCN2A
STXBP1
GNAO1
ARX, DOCK7, SLC25A22, SLC35A2, WWOX
Infantile spasms
ALG13, DNM1, FOXG1 duplications, GABRA1, GABRB3, GRIN1, GRIN2A, GRIN2B, IQSEC2, KCNT1, MAGI2, MEF2C, NEDDL4, NDP, NRXN1, PIGA, PLCB1, PTEN, SCA2, SCN1A, SCN2A, SCN8A, SETBP1, SIK1, SLC25A22, SLC35A2, SPTAN1, ST3GAL3, STXBP1, TBC1D24, TCF4
Lennox-Gastaut syndrome
ALG13, DNM1, FLNA, GABRB3, GLI3, HNRNPU, SCN1A, SCN2A, SCN8A, STXBP1
KCNQ2
KCNT1, PIGQ
Early infantile epileptic encephalopathy (Ohtahara syndrome)
Epilepsy of infancy with migrating focal seizures
KCNT1
SCN2A, SCN1A
PLCB1, QARS, SCN8A, SLC25A22, TBC1D24, SLC12A5
Epilepsy–aphasia spectrum
GRIN2A
Other predominantly myoclonic epilepsies
Onset 0–1 years: EEF1A2, MEF2C, SCN1A, SLC2A1, SPTAN1, SYNGAP1, TBC1D24
Onset >1 year: CHD2, MEF2C, SYNGAP1, UBE3A
Other predominantly focal or multifocal epilepsies
Onset 0–6 months: ARHGEF9, DEPDC5, SCN1A, TBC1D24, PNKP, SLC2A1
Onset 6–12 months: ARHGEF9, DEPDC5, FOXG1 mutations, MBD5, PIGO, SLC13A5
Onset >1 year: ARHGEF9, DEPDC5, MBD5, PCDH19, POLG, TNK2, ZEB2
0 months
3 months
6 months
1 year
2 years
4 years

Treatment for specific genetic epilepsies

- Dravet syndrome due to SCN1A – stiripentol, cannabidiol, fenfluramine, valproate, clobazam, levetiracetam, topiramate, others; DO NOT use medications that block the voltage-gated sodium channel such as phenytoin, carbamazepine, oxcarbazepine, lamotrigine
- SCN2A – medications that block the voltage-gated sodium channel
- SCN8A – medications that block the voltage-gated sodium channel; avoid levetiracetam
- POLG – DO NOT use valproate
- TSC1/TSC2 – vigabatrin, everolimus
- KCNQ2/ KCNQ3 – retigabine, medications that block the voltage-gated sodium channel
- SCL2A1 – ketogenic diet
- ALDH7A1 – pyridoxine
- PNPO – pyridoxine or pyridoxal-5'-phosphate
- GRIN2A – memantine (?)
- CLN2 – cerliponase alfa
- CACNA1A – acetazolamide
- CDKL5 – ganaxolone
- MECP2 – trofinetide
- Gene therapies
- *There are others with a less clear preferred treatment regimen

Objectives

Discuss the rationale and clinical indications for genetic testing in Epilepsy

Review test methodology and limitations for genetic tests including chromosome microarray and next generation sequencing

Understand how to interpret test results in context

Provide examples of specific disorders where a positive result may influence treatment

Recognize the impact of genetics on epileptogenesis and response to medications