Mountain States Regional Genetics Network

The Genetics of Pediatric Seizures and Epilepsy

Amanda G. Sandoval Karamian, MD

9/26/2023

Intermountain® Primary Children's Hospital

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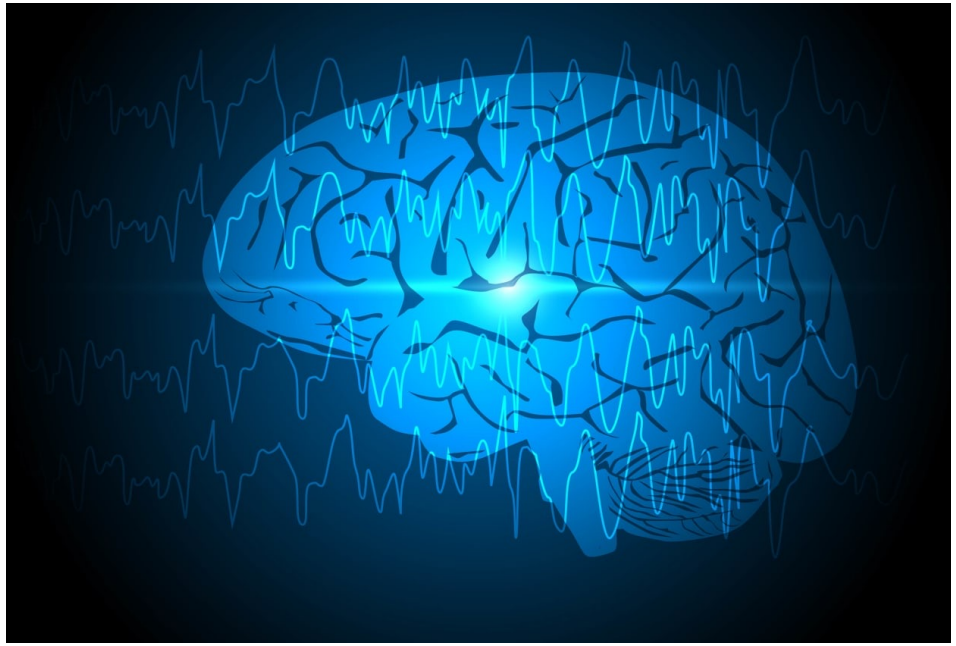
Disclosures

- **No relevant financial disclosures**

Objectives

- Know the definitions of seizures and epilepsy
- Understand the basics of genes and genetic testing
- Understand differing yields of genetic tests
- Know the incidence/prevalence of genetic epilepsy
- Recognize common genetic epilepsies by age of onset



yalemedicine.org, Getty images

Background

Seizures vs Epilepsy

- Seizure – "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain"
- Epilepsy – ILAE Definition

Operational (Practical) Clinical Definition of Epilepsy

1. At least two unprovoked (or reflex) seizures occurring more than 24 hours apart;

2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years;

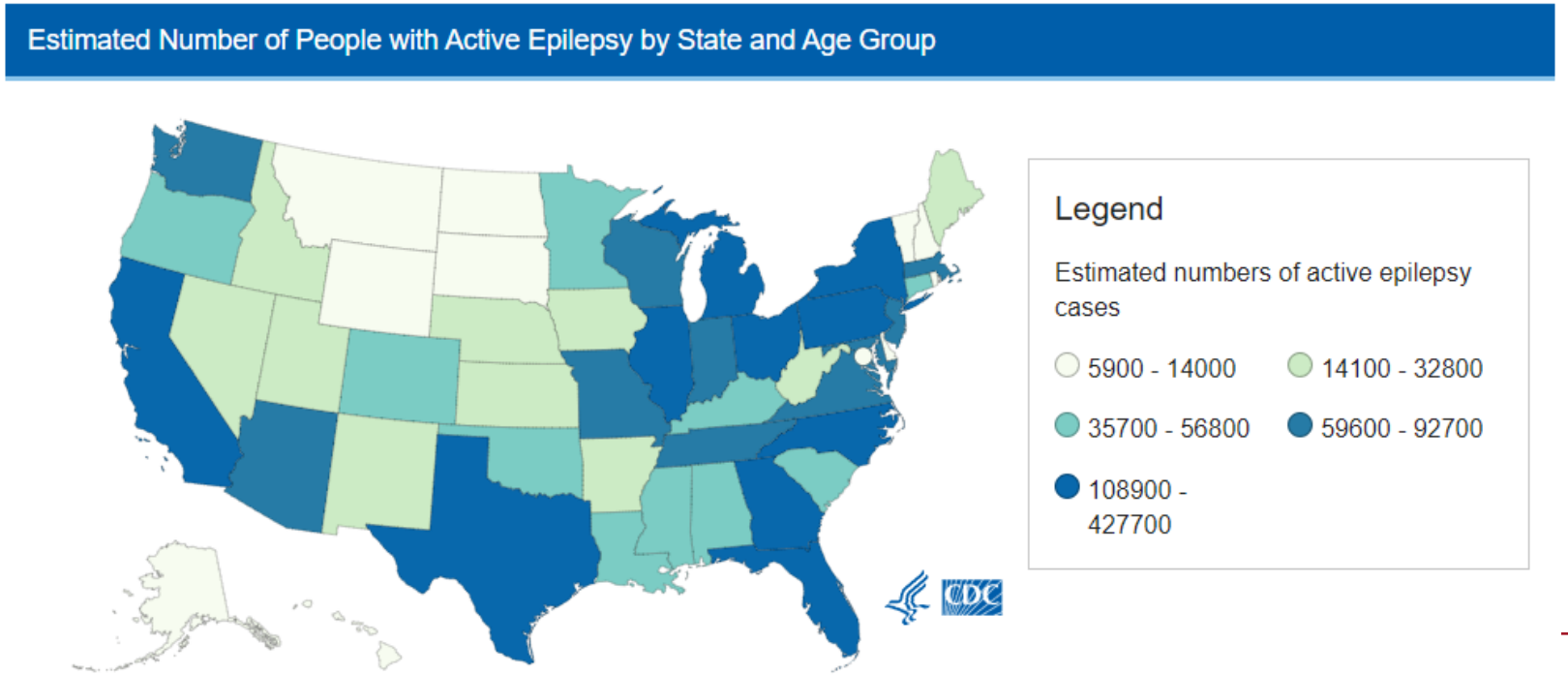
3. Diagnosis of an epilepsy syndrome.

Epilepsy is considered to be resolved for individuals who had age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

Fisher et al, Epilepsia 2017, Fisher et al, Epilepsia 2014

Impact of epilepsy

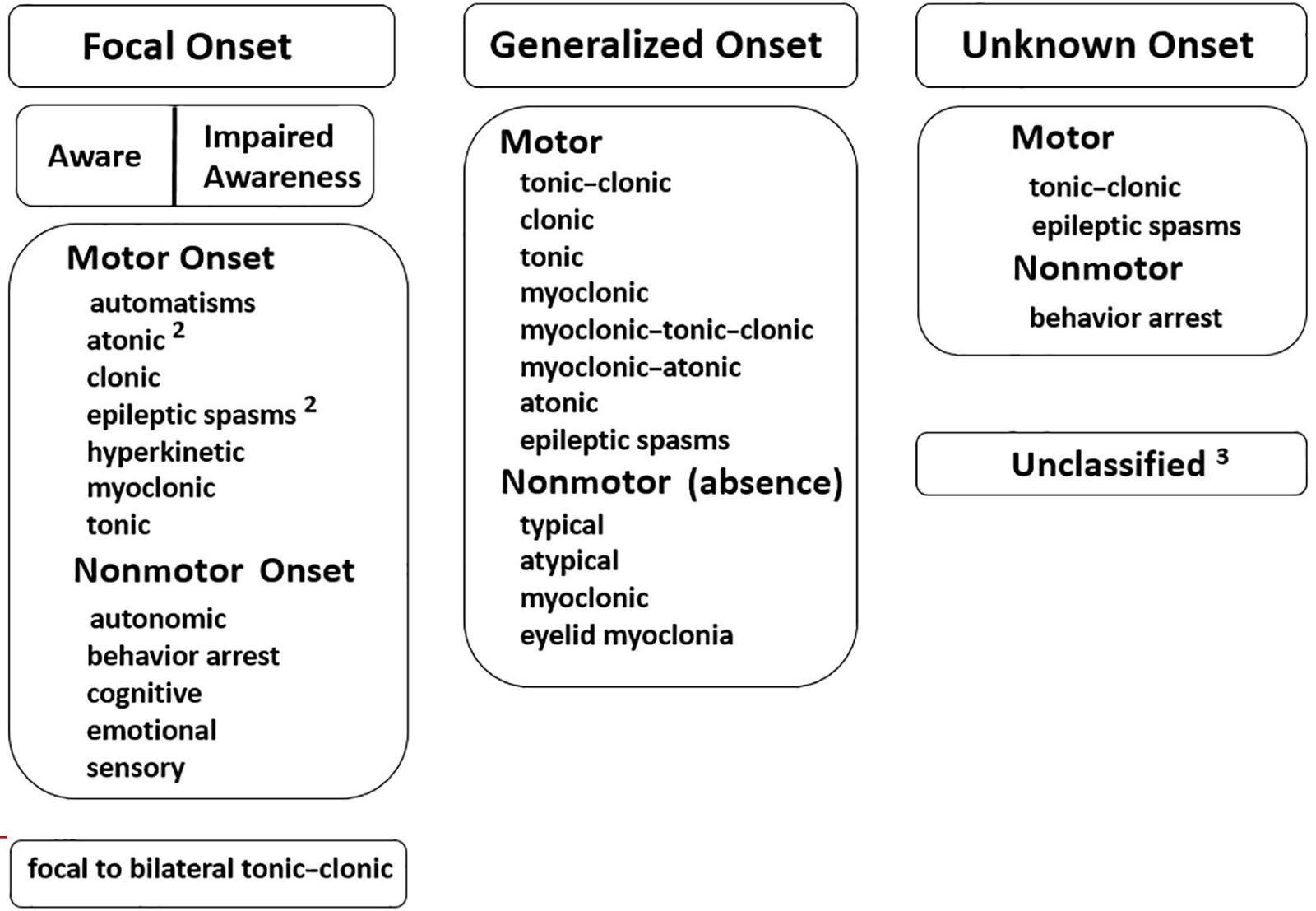
- Epilepsy affects 0.8-1.2% of the general population
- 3.4 million people in the US have epilepsy
- >1 million people in the US have uncontrolled epilepsy
- 470,000 children in the US <14 years old have epilepsy
- 1 in 1000 people with epilepsy die from SUDEP



CDC.gov; Epilepsy Foundation

Seizure Types – any can be seen in genetic epilepsy

ILAE 2017 Classification of Seizure Types Expanded Version [1]



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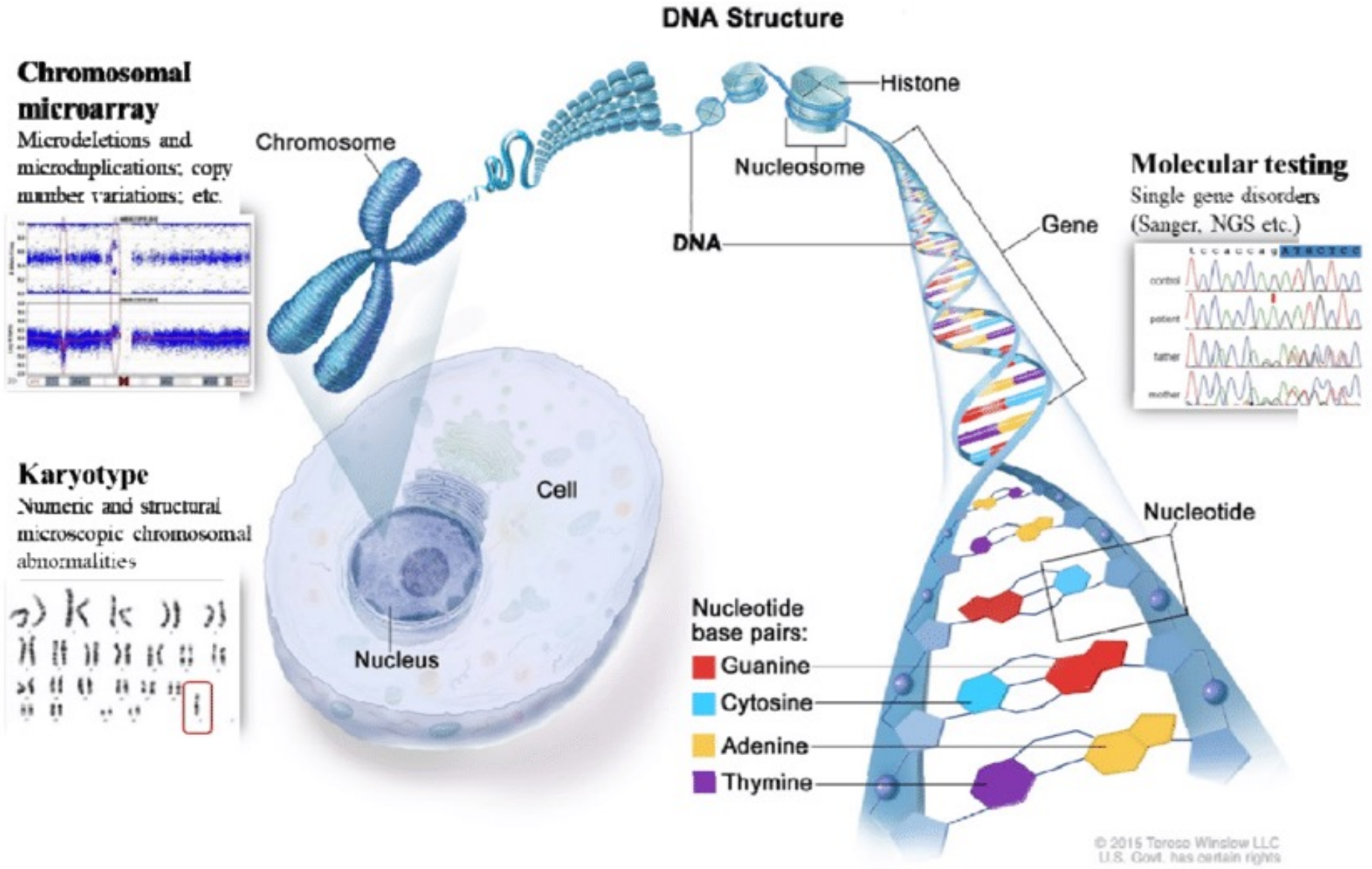
Genes and genetic testing – basics



Jurca-Simina et al, J Pediatrului 2019

Genes and genetic testing – the basics

- Karyotype – number, size, shape of chromosomes, large deletions, duplications, translocations, or inversions
- Chromosomal microarray – smaller deletions and duplications – copy number variants (CNVs)
- Epilepsy gene panels – targeted next generation sequencing (NGS) to simultaneously analyze multiple genes
- Whole exome sequencing (WES) – sequences all coding regions of DNA (exons) using NGS
- Whole genome sequencing (WGS) – sequences all exons and introns of DNA (the entire genome) using NGS, and is able to identify CNVs

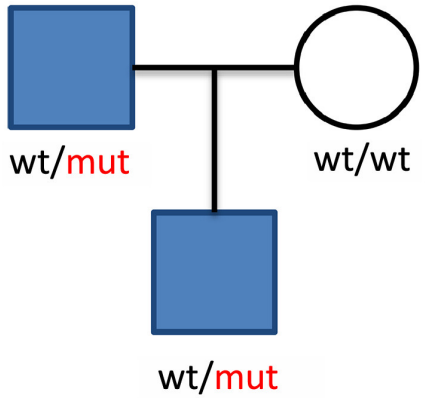
Genes and genetic testing – the basics

If the human genome is a like an instruction manual…

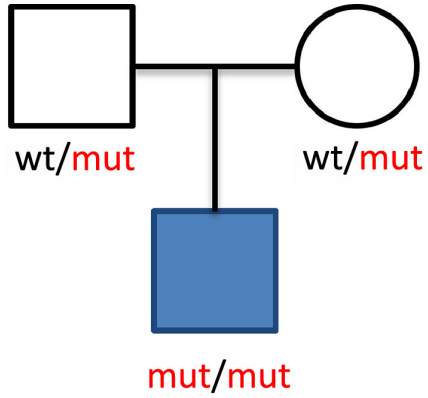
- Karyotype – table of contents
- Chromosomal microarray – looks for changes in paragraphs, sentences, and words
- Epilepsy gene panel – looks for spelling changes in words about a specific topic
- Whole exome sequencing – looks for spelling changes in the main parts of the story
- Whole genome sequencing – looks for spelling changes and changes in paragraphs and sentences from cover to cover

Interpretation of results depends on inheritance pattern

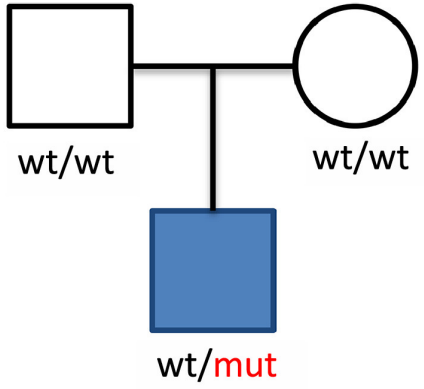
- Most genetic changes resulting in epilepsy are *de novo*



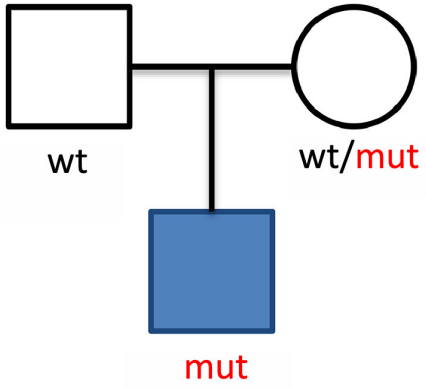
Autosomal dominant inheritance
Example: *CHRNA4, PRRT2, DEPDC5*



Autosomal recessive inheritance
Example: *CSTB, SLC25A22*



***De novo* dominant model**
Example: *SCN1A, STXBP1*



X-linked inheritance
Example: *ARX*

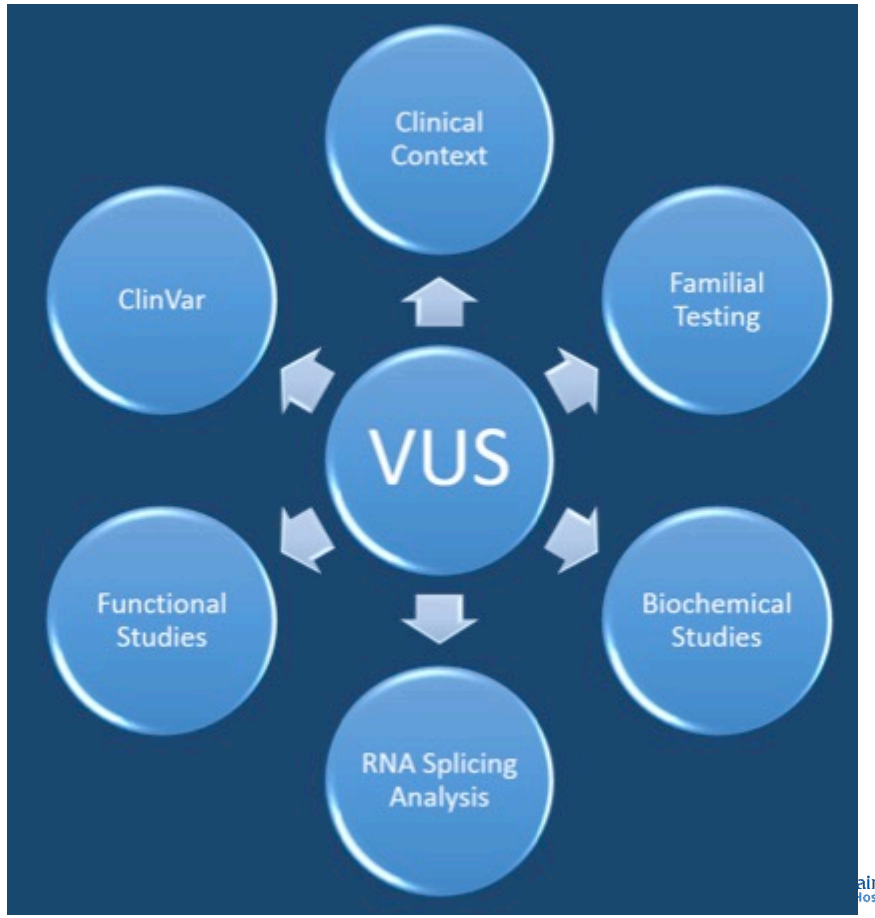
Helbig et al, Epilepsia 2016

Intepretation of results

Positive, Negative and Variants of Uncertain Significance (VUS)

- Clarification of VUS
  - Familial testing
  - Clinical evaluation of phenotype – does it fit?
  - Functional & biochemical testing
  - ClinVar, gnomAD, etc

- A negative or non-contributory test does NOT mean there is not a genetic cause of the epilepsy



Yield of genetic testing in epilepsy

- Karyotype – ~2%, only really for ring chromosomes
- Chromosomal microarray ~8-10%
- Epilepsy gene panel ~20-25%
- Whole exome sequencing ~30-45%
- Whole genome sequencing ~50-60%

- Higher yield in younger age of onset
- Highest yield in developmental and epileptic encephalopathies

Grouping	Subgroup	No. of incl. cohorts	No. of incl. individuals	Diagnostic yield (95% CI)
Overall		103	32 310	23.7% (22%–26%)
By disorder	ASD	14	1530	17.1% (11%–25%)
	Epilepsy	72	27 923	24.0% (22%–27%)
	ID	21	2863	28.2% (22%–35%)
By seizure type	FE	15	1944	15.8% (10%–24%)
	GE	7	1258	24.3% (18%–32%)
	GE & FE	59	26 888	24.8% (22%–28%)
By disorder subtype	Epilepsy without ID	8	1224	9.3% (4%–23%)
	ASD with ID or DD	7	591	24.6% (18%–32%)
	Epilepsy with ID	15	1290	27.9% (24%–33%)
By other DEEs	WS	16	768	19.3% (14%–26%)
	Other DEEs	8	232	38.8% (23%–57%)
By age of onset	Any Age	5	1080	6.6% (2%–22%)
	Childhood	3	171	14.7% (4–42%)
	Neonatal/ Infantile	13	986	29.3% (23%–36%)
By sequencing technology	Panel	73	28 665	22.6% (20%–25%)
	ES	36	3720	27.3% (24%–31%)

Stefanski et al, Epilepsia 2021, meta-analysis of 103 studies through 5/2020

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Cost & time considerations

Genetic testing can be expensive

- Gene panels – though lower yield, often can get free sponsored testing for <9 year olds
- WES – increasingly covered by insurance, but not always
- WGS – previously research-only, then inpatient-only, now more coverage for outpatient testing

Genetic testing takes time

- Gene panels – 2 weeks
- WES – 4-6 weeks
- WGS – 2-3 months

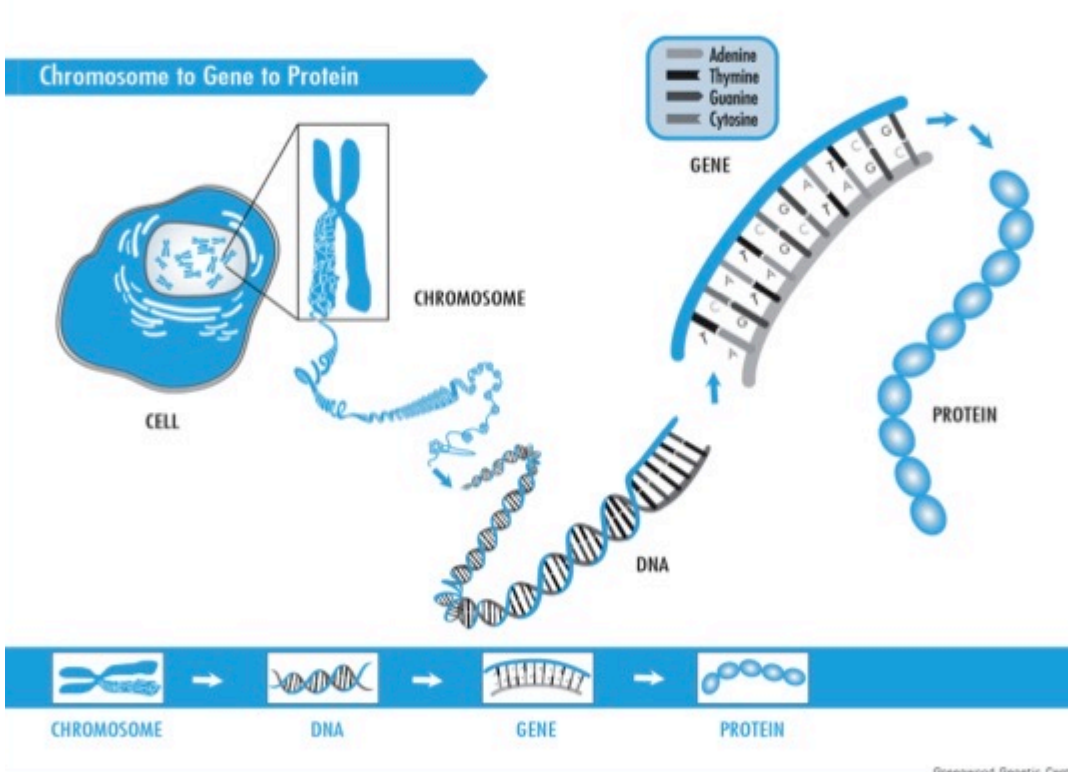
Why do genetic testing for epilepsy?

- Provides a diagnosis for families
- Potential targeted treatments – ie ASO therapy for SCN1A
- Medical management of associated symptoms/conditions – ie cardiac screening
- Prognostic information – regarding epilepsy, development, etc
- Family support groups for rare disorders
- Recurrence risk for families and for future children of patient

Dravet Syndrome Foundation
TSC Alliance
SCN2A-RELATED AUTISM & EPILEPSY FAMILIESCN2A FOUNDATION
KCNT1 EPILEPSY HOPE IS ON THE HORIZON
angelman SYNDROME FOUNDATION
AICARDI SYNDROME FOUNDATION
CCC COALITION TO CURE CHD2
UNIVERSITY OF UTAH
KCNQ2 Cure
CACNA1A FOUNDATION
STXBP1 disorders
SLC6A1 Connect
ring 20 research & support uk

Incidence of genetic epilepsy

- ~20-50% with epilepsy have a genetic etiology identified currently
- Rapidly changing with improved access to more expanded genetic testing
- Many with no known etiology are presumed to be genetic



Greenwood Genetic Center; Beyond the Ion Channel 2016

Increased risk for epilepsy in families

Table I. Incidence and risk for relatives in particular epilepsy syndromes[a]

Epilepsy syndrome	Cumulative incidence by age 40 (%)	Risk for first-degree relatives as standardized incidence ratio (95% CI)
All epilepsy	4.7	3.3 (2.45–4.32)
Idiopathic, all	7.3	5.5 (3.52–7.93)
Postnatal cause, all	2.7	1.8 (0.66–3.14)
Generalized	2.7	5.0 (3.18–7.45)
Generalized, idiopathic	7.3	6.0 (3.75–8.93)
Focal	2.9	2.1 (1.27–3.10)
Focal, idiopathic	2.0	2.7 (0.00–6.81)

CI, confidence interval.
[a]As listed by Peljto et al.[3]

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Helbig et al, Epilepsia 2016, Peljito et al, Brain 2014

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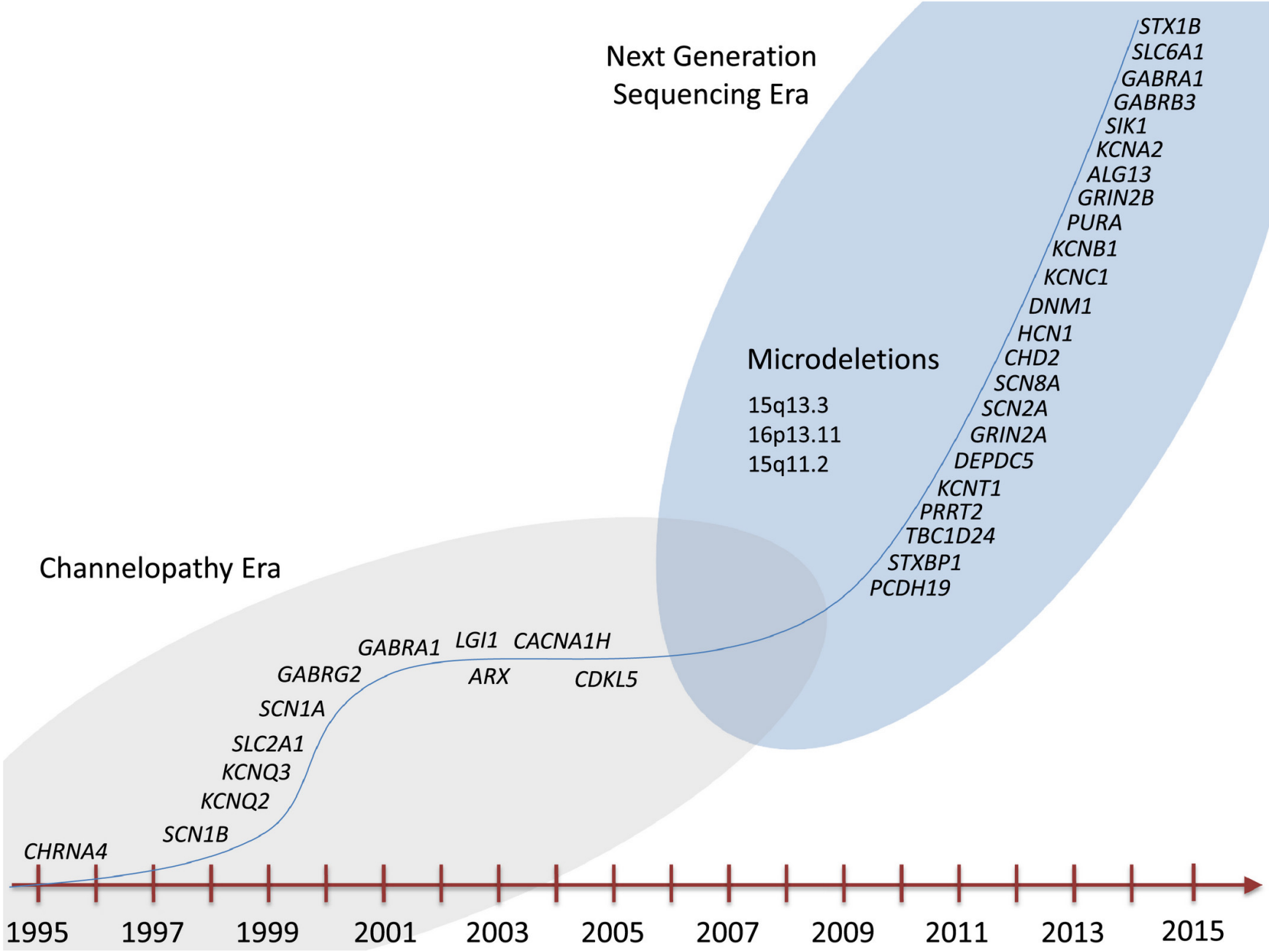
Genetic causes of epilepsy



Helbig et al, Epilepsia 2016

Onset of Epilepsy Syndromes of Childhood

Early Infantile Developmental and Dpileptic Dncephalopathy (EIDEE)
KCNQ2, STXBP1, CDKL5, SCN2A, SLC25A22, ARX, SPTAN1, KCNT1, SEPSECS, ERBB4, SIK1, SCL25A22, PIGA, GABRB2 , SETBP1, STXBP1, GNAO1, DOCK7, SCN8A, UBA5

Self limited familial and nonfamilial
KCNQ2, KCNQ3, SCN2A

Epilepsy of Infancy with Migrating focal seizures
KCNT1 >> SCN1A, SCN2A, PLCB1, TBC1D24, CHD2 , QARS, SCN8A, SLC25A22, SLC12A5, BRAT1

Self limited familial and non-familial infantile epilepsy
PRRT2>>SCN2A, KCNQ2, KCNQ3

Infantile Epileptic Spasms Syndrome
ARX, CDKL5, STXBP1, IQSEC2, TSC1, TSC2, ALG13, DNM1, FOXG1, GABRA1, GABRB3, IQSEC2, KCNT1, MAG12, MEF2C, NEDDL4, NDP, NRXN1, PIGA, PLCB1, PTEN, SCA2, SCN1A, SCN2A, SCN8A, SETBP1, SIK1, SCL25A22, SLC35A2, SPTAN1, ST3GAL3, TBC1D24, TCF4, GNAO1, WWOX

Myoclonic Epilepsy in Infancy (MEI)
No causal genes have been found

Dravet Syndrome
SCN1A>>GABRG2, GABRA1, STXBP1, HCN1, KCNA2, and rare recessive cases with SCN1B

Rasmussen's encephalitis
Thought to be an autoimmune process – no known genes

Genetic Epilepsy with Febrile Seizures Plus (GEFS+)
SCN1A, SCN1B, STX1B, HCN1

Epilepsy with myoclonic absences
Thought to be genetic with only isolated case reports of specific gene defects

Epilepsy with eyelid myoclonia
No known genes

Febrile Infection-Related Epilepsy Syndrome (FIRES)
No known genes

Childhood absence epilepsy
GABRG2, GABRA1, SLC2A1 (GLUT 1 deficiency), PRRT2, CACNA1A Complex inheritance: 20% have a first degree relative with seizures

Epileptic encephalopathy with continuous spike and wave during sleep
A family history is uncommon, GRIN2A mutations described

Lennox Gastaut Syndrome
Mutations in many genes have been associated and usually de novo: *ALG13, DNM1, FLNA, GABRB3, GLI3, HNRNPU, SCN1A, SCN2A, SCN8A, STXBP1*

Epilepsy with myoclonic atonic seizures
SCN1A, SCN1B, SCN2A, STX1B, SLC2A1, CHD2, SYNGAP1, KIAA2022, SLC6A1, GABRA1, GABRG2

Familial focal epilepsy with variable foci
DEPDC5, NPRL2, NPRL3

Mesial temporal lobe epilepsy
Often not tested, *DEPDC5, SCN1A, SCN1B and LGI1*

Sleep related-hypermotor epilepsy
CHRNA4, CHRNB2, CHRNA2, KCNT1 , DEPDC5, NPRL2, NPRL3, PRIMA1

Hypothalamic hamartoma
Most sporadic, 5% with *GL13* mutation

Neonatal Syndromes → Infantile Syndromes → Childhood Syndromes

*Mitochondrial disease is explained in the text

Yozawitz & Moshe, Acta Epileptologica 2022

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Common genetic epilepsies

Neonatal

- Early Infantile Developmental and Epileptic Encephalopathy (EIDEE)
  - Genetic etiology identified in >50%
  - **KCNQ2, SCN2A**, SCN8A, STXBP1, CDKL5, KCNT1, UBA5
- Self-limited neonatal epilepsy (SeLNE)
  - **KCNQ2, KCNQ3**, SCN2A

Zuberi et al, Epiepsia 2022; Yozawitz & Moshe, Acta Epileptologica 2022

Common genetic epilepsies

Infantile

- Self-limited familial neonatal-infantile epilepsy (SeLFNIE)
  - **SCN2A**, KCNQ2
- Self-limited infantile epilepsy (SeLIE)
  - **PRRT2**, SCN8A, SCN2A
- Myoclonic epilepsy in infancy (MEI)
  - No known causal genes, but FHx febrile seizures in ~10%
- Genetic epilepsy with febrile seizures plus (GEFS+)
  - **SCN1A**, SCN1B, STX1B, HCN1
- Epilepsy of infancy with migrating focal seizures (EIMFS)
  - **KCNT1**, SCN1A, SCN2A, SLC12A5, BRAT1, TBC1D24
- Infantile epileptic spasms syndrome (IESS)
  - Genetic etiology in up to 41% of cases – Trisomy 21, ARX, CDKL5, STXBP1, IQSEC2, TSC1, TSC2
- Dravet Syndrome (previously severe myoclonic epilepsy of infancy)
  - **SCN1A in 80-85%**, GABRG2, GABRA1, STXBP1, SCN1B

Common genetic epilepsies

Childhood

- Epilepsy with myoclonic-atonic seizures (Doose syndrome) – SCN1A, SLC2A1, SCN1B, SCN2A, SLC6A1, GABRG2, GABRA1
- Epilepsy with eyelid myoclonia (Jeavons) – none known, likely polygenic; CHD2, SYNGAP1, NEXMIF when with DEE
- Lennox-Gastaut Syndrome – many, SCN1A, SCN2A, SCN8A, STXBP1, FLNA, GABRB3, ALG13, etc
- Childhood absence epilepsy – GABRG2, GABRA1, SCL2A1 ***GLUT1 Deficiency**
- Epilepsy with myoclonic absence (EMA)– none well established, likely polygenic
- Self-limited epilepsy with autonomic seizures (SeLEAS); formerly Panayiotopolous syndrome – likely polygenic, rare SCN1A
- Childhood occipital visual epilepsy (COVE; childhood occipital epilepsy Gastaut type) – likely polygenic, FHx+ in 1/3
- Photosensitive occipital lobe epilepsy (POLE) – likely polygenic, possible GRIN2A, FHx+ in 1/3
- Self-limited epilepsy with centrotemporal spikes (SeLECTS; BECTS, CECTS, Benign Rolandic) – likely polygenic, GRIN2A
- Epileptic encephalopathy with spike-and-wave activation in sleep (EE-SWAS/DEE-SWAS)– GRIN2A
- Autosomal dominant nocturnal frontal lobe epilepsy – CHRNA4, CHRNB2, CHRNA2, DEPDC5
- Hypothalamic hamartoma – 5% with GL13

Specchio et al, Epiepsia 2022; Yozawitz & Moshe, Acta Epileptologica 2022

Common genetic epilepsies

Adolescence

- Juvenile absence epilepsy – likely polygenic, GABRG2, GABRA1, SLC2A1, CACNA1A
- Juvenile myoclonic epilepsy – likely polygenic
- Epilepsy with generalized tonic-clonic seizures alone – likely polygenic
- Epilepsy with auditory features (EAT) – LGI1, RELN, MICAL1
- Familial temporal lobe epilepsies – DEPDC5, SCN1A, SCN1B, LGI1
- Familial focal epilepsy with variable foci (FFEVF) – DEPDC5, NPRL2, NPRL3, TSC1, TSC2

Hirsch et al, Epilepsia 2022; Riney et al, Epilepsia 2022

Examples of genes and their phenotypes

PRRT2

- **Benign Familial Infantile Seizures (BFIS)** – AD, clusters of focal seizures or generalized tonic-clonic seizures between 3-12 months, usually self-limited and remit ~24 mos, usually normal development

- **Paroxysmal Kinesogenic Dyskinesia (PKD)** – AD, brief attacks of hyperkinetic movements (dystonia, chorea, athesosis) precipitated by sudden movements

- **Infantile Convulsions with Choreoathetosis (ICCA)** – AD, combination of infantile seizure and paroxysmal kinesogenic dyskinesia

- **Other phenotypes:** ~5% with other phenotypes including various movement disorders, epilepsies, hemiplegic migraine, and developmental delay and intellectual disability

- Presynaptic protein (proline-rich transmembrane protein 2) interacting with the SNARE complex, namely SNAP25, involved in synaptic vesicle fusion

SCN1A

- **Dravet Syndrome** - severe childhood epilepsy with prominent fever-associated seizures, progresses to multiple seizure types (myoclonic, focal), and associated with progressive cognitive and behavioral deficits
- **GEFS+** - milder with broad phenotypic range from unaffected carriers to simple febrile seizures, febrile seizures plus, and sometimes more severe epilepsies; febrile seizures persist beyond 6 y/o or also have afebrile seizures
- **Febrile seizures** – Susceptibility gene for febrile seizures
- **Treatment implications**
  - Sodium channel medications are typically contraindicated in SCN1A-related epilepsies, particularly such agents as phenytoin, carbamazepine, oxcarbazepine, and lamotrigine
  - Effective treatments: valproic acid, cannabidiol, fenfluramine, stiripentol, clobazam, topiramate, ketogenic diet
  - Genetically based therapies under investigation – antisense oligonucleotide therapies

STK-001 – ASO for SCN1A Dravet Syndrome

Reductions in Convulsive Seizure Frequency Were Observed Across Dose Cohorts*

Median % Reduction From Baseline In Convulsive Seizure Frequency	30mg MAD (3 Doses, N=18)	45mg MAD (3 Doses, N=16)	70mg MAD** (3 Doses, N=5) (2 Doses, N=6)
At 3 Months After Last Dose	27% (N=16)	19% (N=14)	80% (N=6†)
At 6 Months After Last Dose	4% (N=13)	45% (N=8)	89% (N=3†)
Day 29 **Through 3** Months After Last Dose	28% (N=17)	18% (N=16)	42% (N=8†)
Day 29 **Through 6** Months After Last Dose	24% (N=16)	26% (N=14)	42% (N=6†)

* Patient numbers were primarily variable due to the fact that patients with ≧50% of the data points in each time period were included in the applicable "through" cohort (bottom two data rows), even if the patient had not yet reached the last timepoint in the time period.

** ADMIRAL patients only. The MONARCH study is evaluating single doses of 70mg and data from this cohort are not yet available.

†5/6 patients (at 3 months), 3/3 patients (at 6 months), 5/8 patients (day 29 through 3 months) and 5/6 patients (day 29 through 6 months) after last dose were treated with 3 doses of 70mg

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Stoke Therapeutics Press Release, July 25, 2023

KCNQ2

- **Benign familial Neonatal Epilepsy (BFNE) –** seizure onset in the first week of life in an otherwise healthy infant; usually brief tonic, clonic, apneic or autonomic seizures which resolve during the first year of life
  - normal development
  - ~10% of develop epilepsy later in life

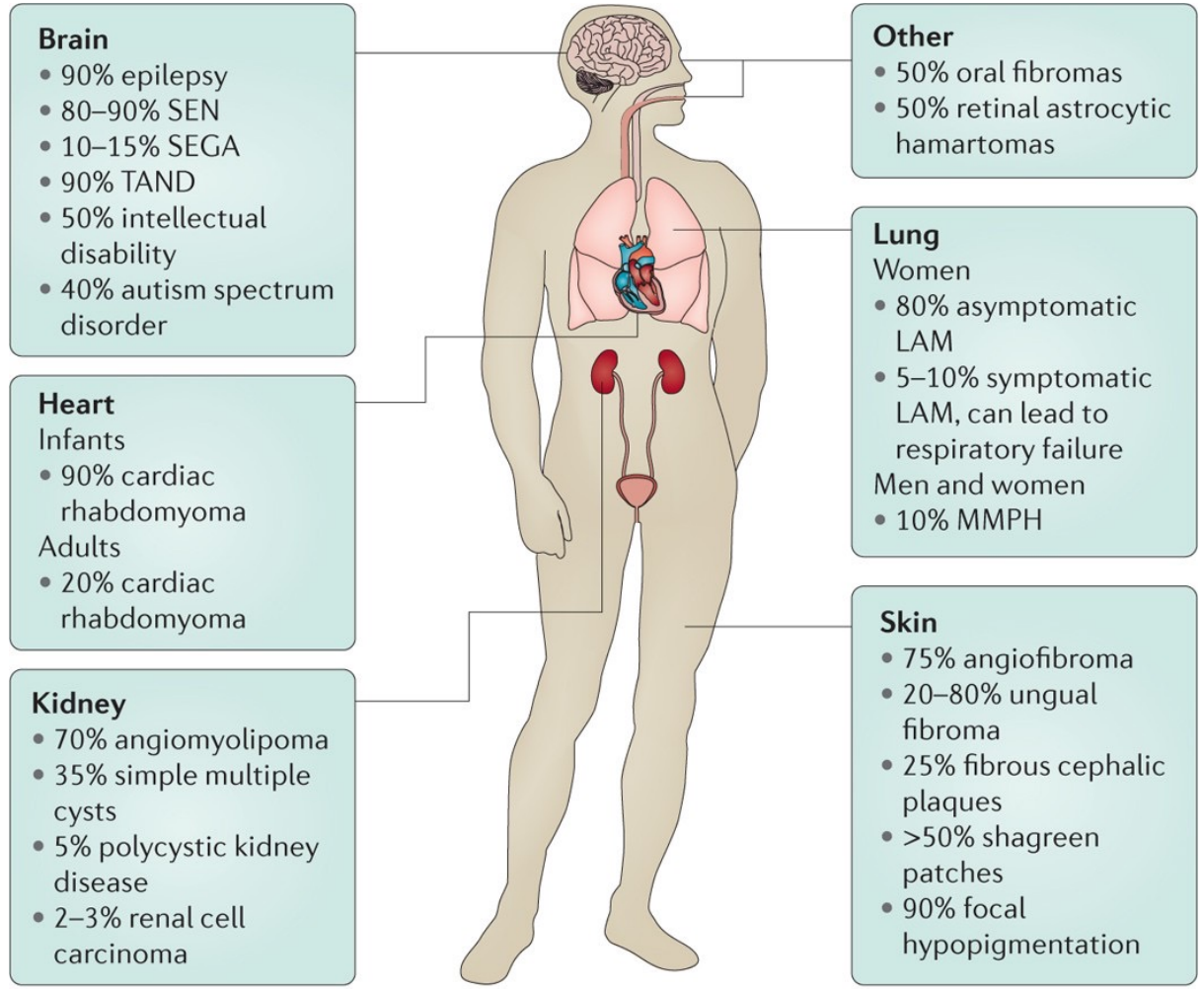
- ***KCNQ2* related EIDEE -** neonates present seizures (usually tonic) which are difficult to control
  - + developmental delay
  - interictal EEG can be abnormal, showing a burst suppression pattern or multifocal abnormalities
  - seizure frequency decreases in time, with poor developmental outcome and intellectual disability ranging from mild to profound

- ***KCNQ2* and infantile spasms -** few patients described with de novo KCNQ2 mutations and infantile spasms with onset in the first year of life

- Encodes a subunit of a voltage-gated potassium channel mainly expressed in the neurons and forms heterotetrameric channels with KCNQ3 that are responsible for the M-current, which determines the excitability of neurons and their response to synaptic input

TSC

- Variable neurocutaneous disorder
- Benign tumors or hamartomas of multiple organs including the brain, eyes, heart, lung, liver, kidney, and skin
- Seizures are common, occur in >80%
- Seizures typically start at 3-5 months of age, neonatal presentation in up to 6%
- Infantile spasms occur in up to 35%
- >50% have cognitive deficits and learning disabilities, with 2/3 having moderate to severe impairment, and 1/3 having mild to moderate impairment
- Autism, behavioral problems, and psychosocial difficulties are common



Nature Reviews | Disease Primers

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Henske et al, Nature Reviews Disease Primers 2016

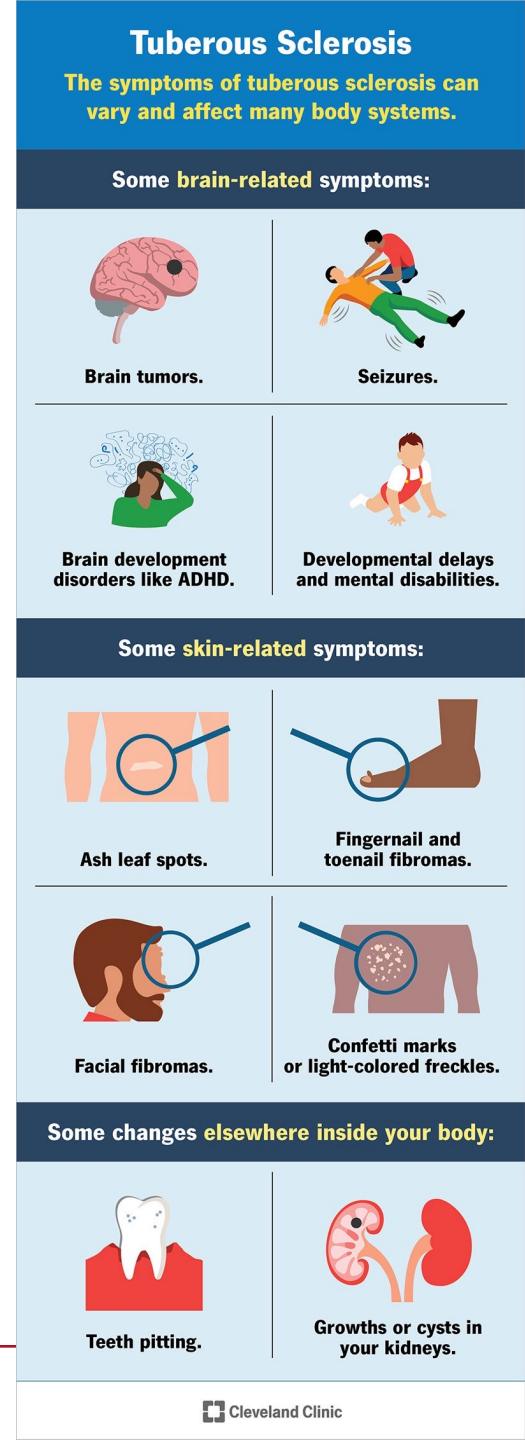
TABLE 2.
Diagnostic Criteria

Major Criteria	Minor Criteria
Hypomelanotic macules (≥3; at least 5 mm diameter)	"Confetti" skin lesions
Angiofibroma (≥3) or fibrous cephalic plaque	Dental enamel pits (≥3)
Ungual fibromas (≥2)	Intraoral fibromas (≥2)
Shagreen patch	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts
Multiple cortical tubers and/or radial migration lines	Nonrenal hamartomas
Subependymal nodule (≥2)	Sclerotic bone lesions
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
LAM*	
Angiomyolipomas (≥2)*	

Abbreviations:
LAM = Lymphangiomyomatosis
TSC = Tuberous sclerosis complex
Definite TSC: 2 major features or 1 major feature with 2 minor features.
Possible TSC: either 1 major feature or ≥2 minor features.
Genetic diagnosis: A pathogenic variant in *TSC1* or *TSC2* is diagnostic for TSC (most TSC-causing variants are sequence variants that clearly prevent TSC1 or TSC2 protein production. Some variants compatible with protein production [e.g., some missense changes] are well established as disease-causing; other variant types should be considered with caution).

* A combination of the 2 major clinical features LAM and angiomyolipomas without other features does not meet criteria for a definite diagnosis.

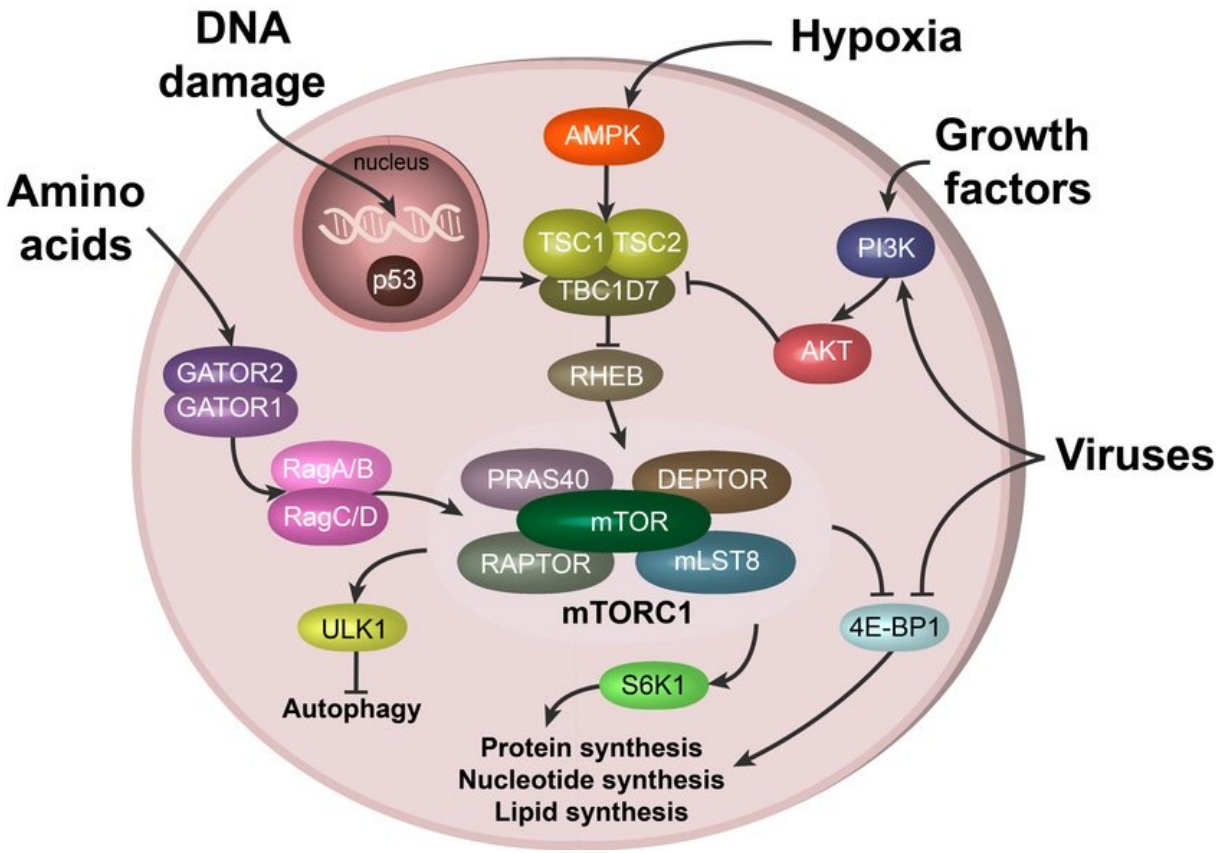
Northrup et al, Pediatric Neurology 2021



GATOR Complex Genes

DEPDC5, NPRL2, NPRL3

- DEPDC5 – encodes subunit of GATOR1 complex, regulates mTOR pathway, 50-80% penetrance
  - Familial epilepsy with variable foci, can have focal cortical dysplasias
  - AD nocturnal frontal lobe epilepsy
  - Familial mesial temporal lobe epilepsy
- NPRL2 & 3 – encode subunits of the GATOR1 complex, regulates mTOR pathway
  - Familial epilepsy with variable foci
  - Focal cortical dysplasias



Akbay et al, Cells 2020

Genetics of febrile seizures

- Febrile seizures run in families
- Likely a genetic predisposition, but not commonly tested
- Large genome-wide association study of patients with febrile seizures in 2014
- SCN1A, SCN2A, and ANO3 associated with febrile seizures – sodium and chloride channels
- IFI44L, CD46 associated with seizures after vaccination – immune response genes

- Limited data on utility of testing in this population

Feenstra et al, Nat Genet 2014

Summary

- Genetic causes of seizures and epilepsy are common and being increasingly identified
- Genetic testing yield for epilepsy is highly dependent on the test type
- Getting a diagnosis is useful for prognosis, family support, and family planning
- There are specific treatments available for a subset of genetic epilepsy
- Common genetic epilepsy syndromes can be categorized by age of onset

Questions?

THANK YOU

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