Practical Use of Genetic Testing in Epilepsy Management

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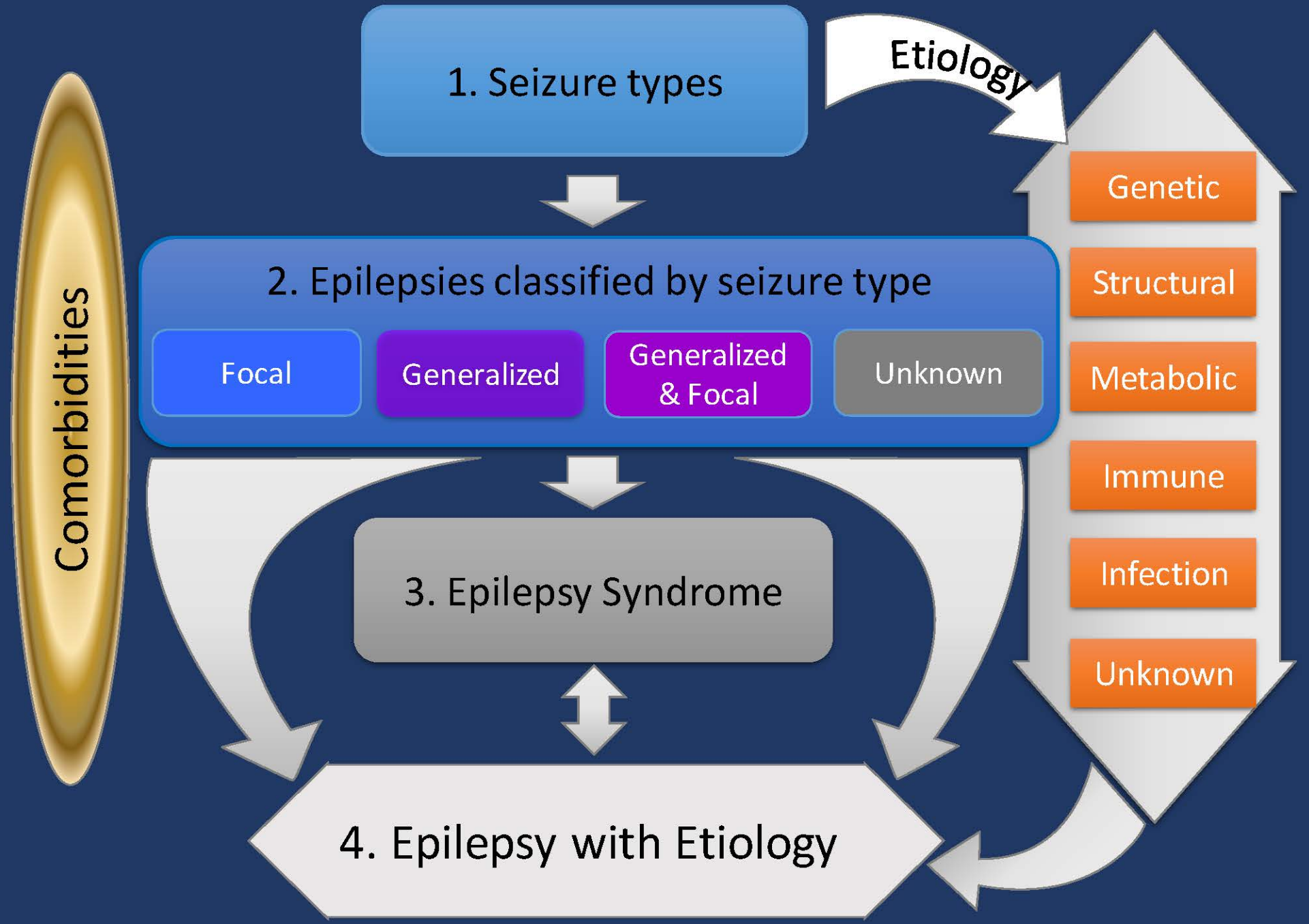
Introduction

- Epilepsy is one of the most common neurological diseases
- The management of epilepsy is generally based on
  - Age of the patients
  - Seizure types
  - EEG
  - Imaging result
- Causes of epilepsy are diverse

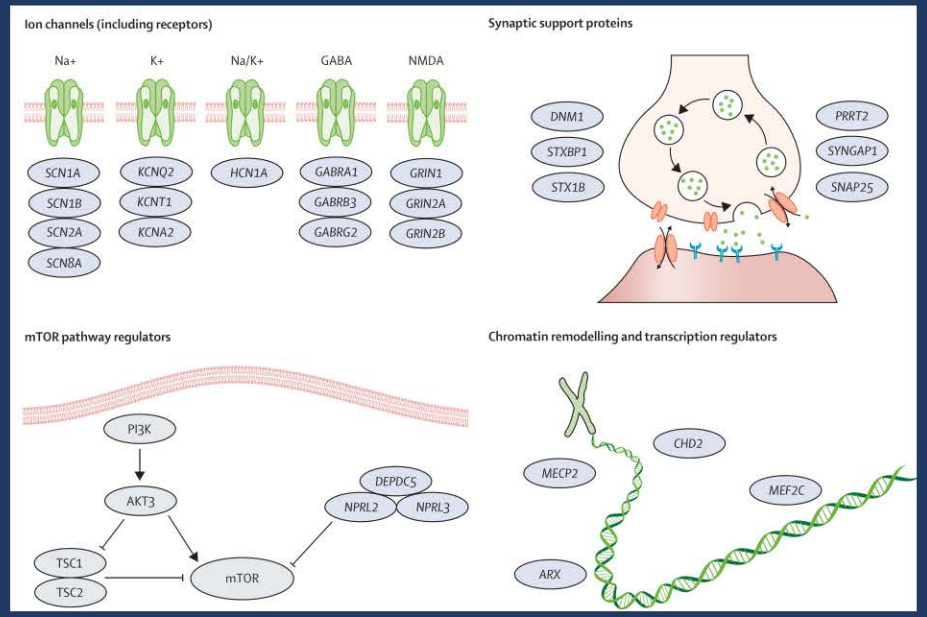

1. Seizure types
Etiology
Genetic
Structural
Metabolic
Immune
Infection
Unknown
Comorbidities
2. Epilepsies classified by seizure type
Focal
Generalized
Generalized & Focal
Unknown
3. Epilepsy Syndrome
4. Epilepsy with Etiology

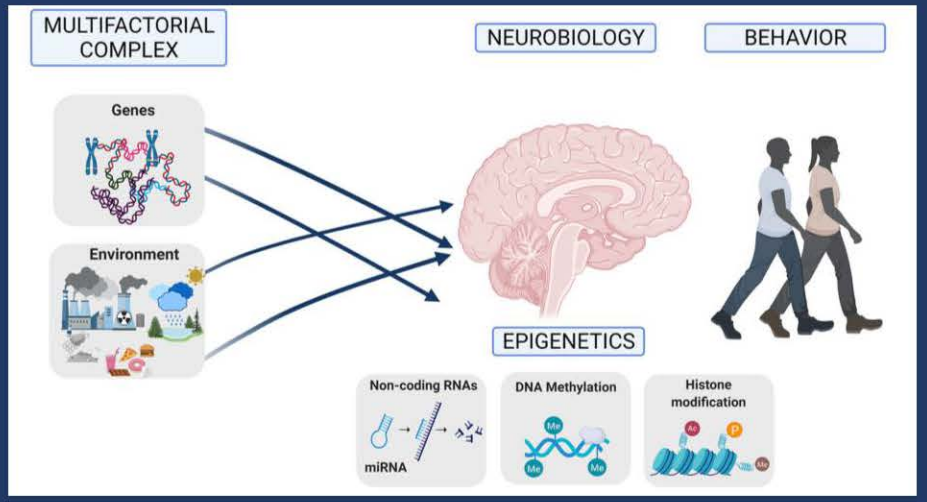
Genetic epilepsy

- A known or presumed underlying genetic etiology
  - lack of an acquired cause, such as trauma or infection
  - seizures are the core symptom of the disorder
- The genetic defect may arise at a chromosomal or molecular level.
- It is important to emphasize that "genetic" does not mean the same as "inherited" as de novo mutations are not uncommon.

Genetic principles

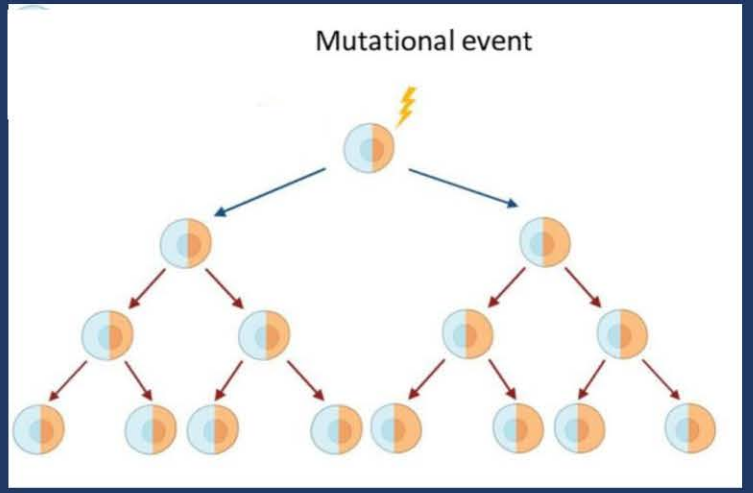
- Monogenic epilepsies
  - Single or monogenic epilepsy
  - Various cellular function
  - Main interest in genetic epilepsies
- Epilepsies with complex genetic patterns
  - Multifactorial etiology which likely
    - Oligogenic or polygenic
    - Affected by
      - Environment
      - Epigenetic factors
        - changes in gene activity and expression

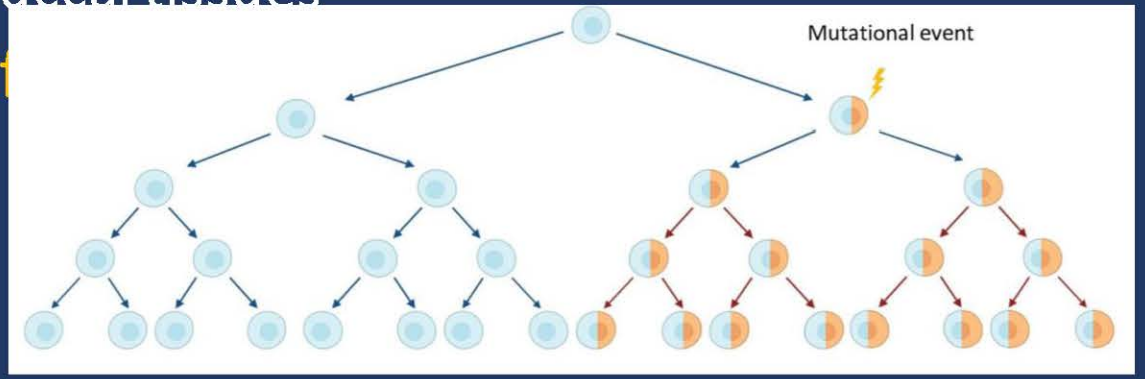




Monogenic epilepsy

- Caused by variation in a single gene defects
- AD, AR, X-linked, mitochondrial
- May caused by
  - Germline variants: variants in eggs an sperm cells
    - Inherited, de novo
    - All tissues are affected
    - Mutation can be detected by blood or buccal tissues
  - Somatic variant: present only in specif
    - Usually de novo
    - Mutation can only be detected by some tissues (brain)

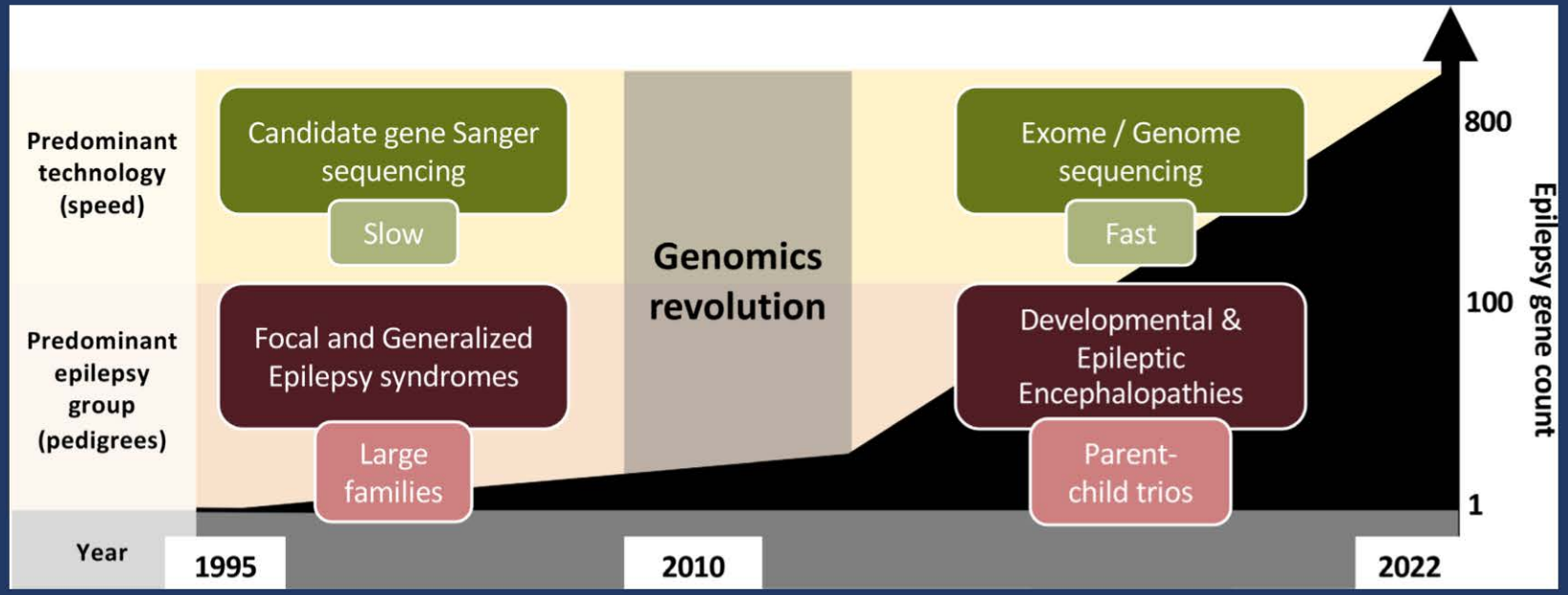




Gerasimenko A, et al. Neurobiology of Disease 2023;182

How many epilepsy genes are there?

- First established gene is *CHRNA4* in 1995
- More than 1000 genes are found to be associated with epilepsy with the discovery of WES/WGS
- Most epilepsy genes (90%) are associated with DEE phenotype



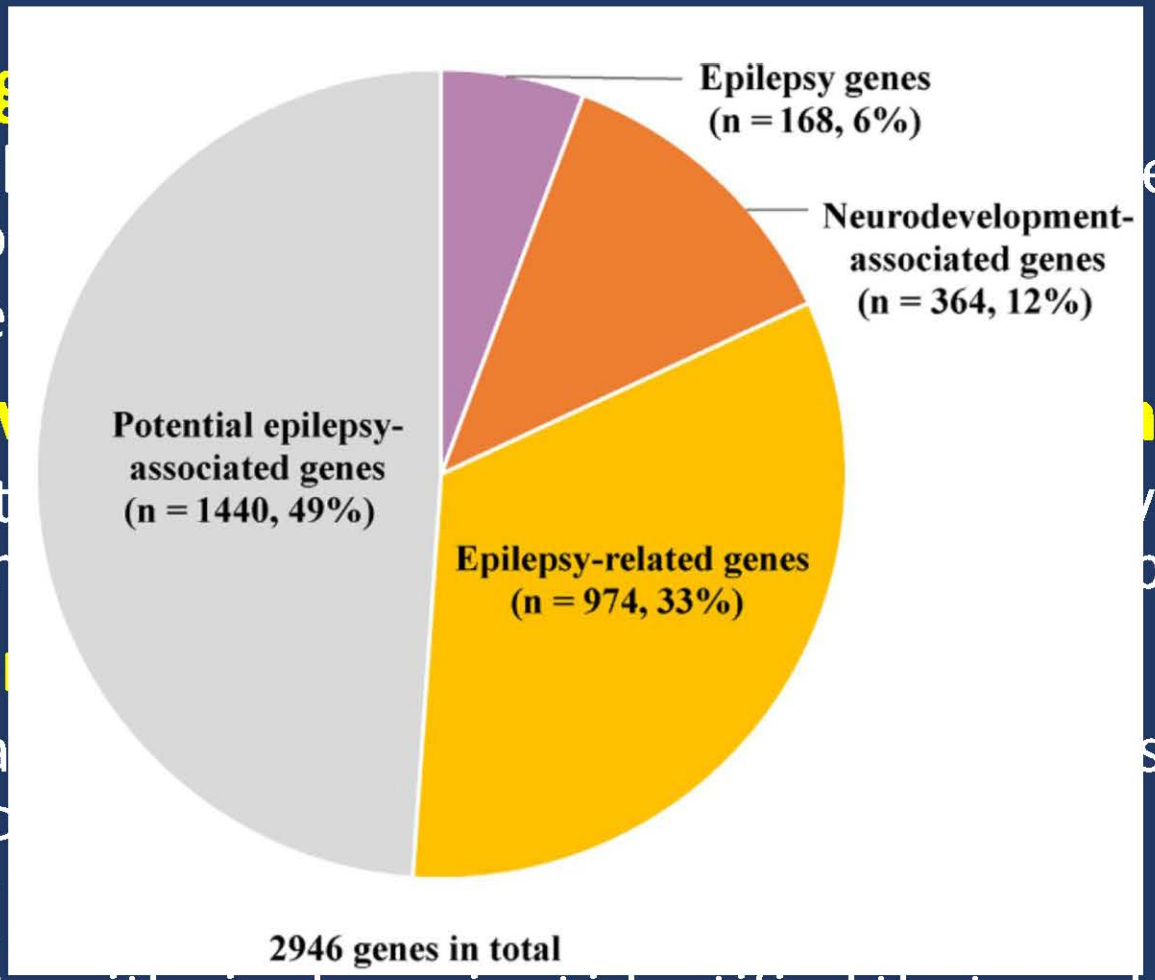
Oliver KL, et al. Epilepsia. 2023;64:1368–1375

Resource

- https://github.com/bahlolab/genes4epilepsy
  - Last update March 2024
  - 998 gene listed

Categories of genes with epilepsy

- **Epilepsy g**
  - genes t epsies as pure or core sympto
  - May be
- **Neurodev es**
  - Genes t velopmental malforn by epilepsy or seizures
- **Epilepsy-**
  - genes a stemic abnormalities and acc
- **Potential**
  - Majority with single variant identified that need further validation



Zhang MW, et al. Seizure 2024;116:4-13

Why do we need genetic tests in epilepsy

- What we/patients get from the test?
- Whom to test?
- Pre-counseling needed?
- Which genetic tests?

What we/patients get from the test?

- Accurate Diagnosis
- Treatment Plans
- Participation in Research and Clinical Trials
- Understanding Comorbidities
- Prognosis
- Risk Assessment for Family Members

Sheidley BR, et al. Epilepsia 2022;63:375-387

What we/patients get from the test?

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- Avoid excessive investigation
- Cost effectiveness
- Decrease guilty

Sheidley BR, et al. Epilepsia 2022;63:375-387

Characteristic	Total ($n=28$)	EGT ($n=8$)	LGT ($n=20$)
Initial genetic test performed, *n* (%)			
MEP	15 (53)	7 (87)	8 (40)
CMA	6 (21)	0 (0)	6 (30)
Karyotype	3 (11)	1 (13)	2 (10)
Single-gene panel	1 (4)	0 (0)	1 (5)
Other	3 (11)	0 (0)	3 (15)
Metabolic serum/urine testing, *n* (%)	16 (57)	0 (0)	16 (80)
Invasive procedure (LP), *n* (%)	5 (18)	0 (0)	5 (25)
Epilepsy-related unscheduled hospitalizations			
Average	1.9	1.5	2.0
Median	1.5	1.0	1.5
Range	0–12	0–3	0–12
Epilepsy-related ED visits			
Average	4.3	3.1	4.8
Median	3.0	3.0	3.0
Range	0–20	1–6	0–20
Clinical management changes due to MEP results, *n* (%)			
Initiation of medication	5 (18)	1 (13)	4 (20)
Discontinuation of medication	1 (4)	0 (0)	1 (5)
Avoidance of certain medication classes	1 (4)	1 (13)	0 (0)
Referral to a specialist	3 (11)	0 (0)	3 (15)
None	18 (64)	6 (75)	12 (60)

(A)						(B)				
Pathway	Step 1	Step 2	Step 3	Step 4	Step 5	Total cost	Diagnoses made	Average cost per diagnosis	Cost per patient	ICER relative to Pathway 1
1	Tier 1	Tier 2	Repeat MRI	Tier 3	—	$661 103	39	$16 951	$7687	—
2	Tier 1	Tier 2	Repeat MRI	Tier 3	WES	$738 136	48	$15 378	$8583	$8559
3	Tier 1	Tier 2	Repeat MRI	WES	Tier 3	$690 356	48	$14 382	$8027	$3250
4	Tier 1	Tier 2	WES	Repeat MRI	Tier 3	$693 951	48	$14 457	$8069	$3650
5	Tier 1	WES	Tier 2	Repeat MRI	Tier 3	$677 081	48	$14 106	$7873	$1775
6	Tier 1	WES	Repeat MRI	Tier 2	—	$553 431	48	$11 530	$6435	Pathway 6 dominates Pathway 1[a]
7	Tier 1	WES	Repeat MRI	—	—	$455 597	46	$9904	$5298	Pathway 7 dominates Pathway 1[a]

- Early testing is associated with
- Fewer non-diagnostic tests
- Fewer invasive procedures
- Reduced estimated healthcare-related

Smartwood SM, et al. Epilepsia Open. 2024;9:439–444.
de Lange IM, et al. Epilepsia 2018;59:1154-1165

What we/patients get from the test?

- Accurate Diagnosis
- Treatment Plans
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- Understanding Comorbidities
- Prognosis
- Risk Assessment for Family Members

- Precision medicine
- What to give and avoid

Sheidley BR, et al. Epilepsia 2022;63:375-387

Types of treatment	Gene	Treatment
Substitutive therapies	SLC2A1 (GLUT1)	Ketogenic diet
	ALDHT7A1	B6
	PNPO	P5P
	TPP1 (CLN2)	Cerliponase alfa
	FOLR1	Folinic acid
	BTD	Biotin
Modifying pathway	mTOR complex (including TSC)	Rapamycin
	DEPDC5	
Function-based therapies	KCNQ2	GBP, RET
	KCNT1	Quinidine (not consistent)
	GRIN1A	Memantine
	GARRB3	Metformin
	PCDH19	Ganaxolone/neurosteroids
	GAD1	VBG, KD

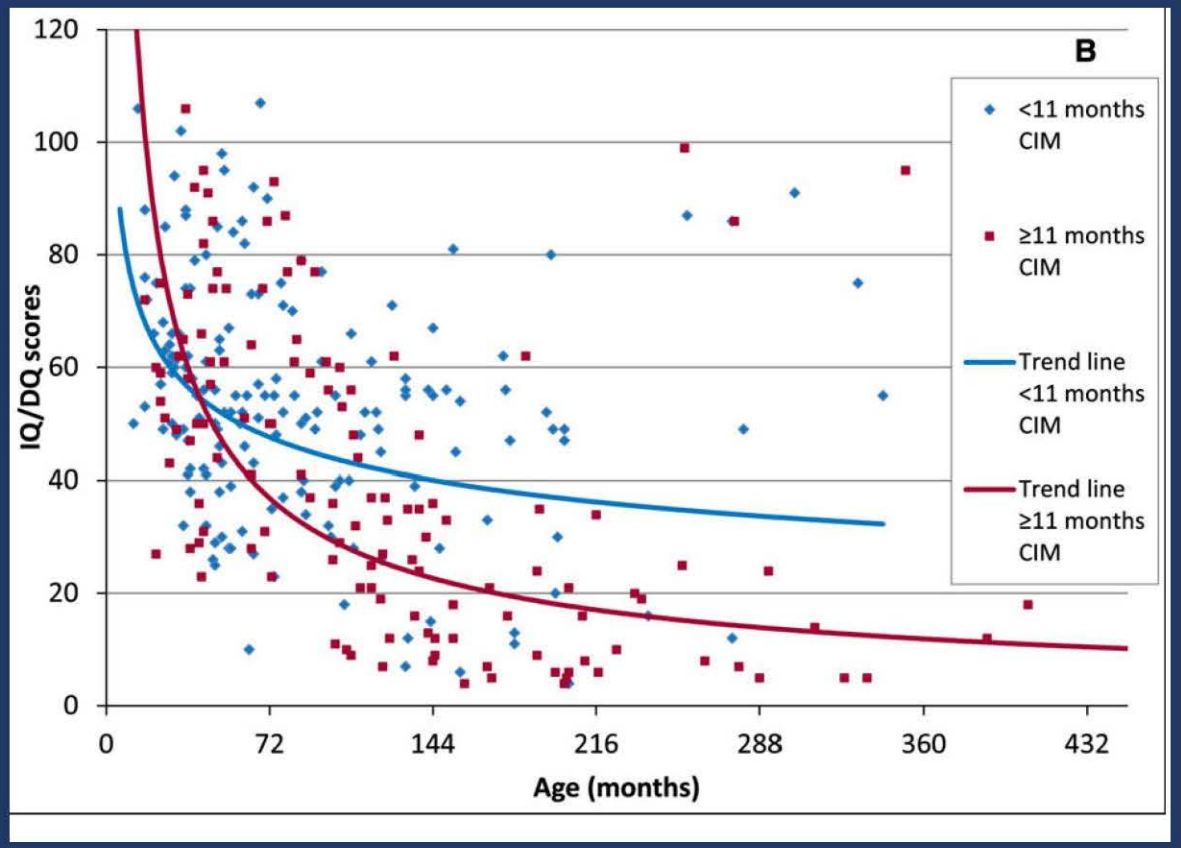
Marini C, Giardino M. Br J Clin Pharmacol 2022;88:2539-2551

	Functional pathogenic mechanism	Epilepsy syndrome	Effective treatment	Contro-indicated treatment
SCN1A Nav1.1	LoF	DS	GABAergic agents (VPA, CLB, STP), TPM, CBD, FEN, ETS, LEV, ZNS, PER, BROM, KD, VNS	SCBs (CBZ, OXC, PHT, LGT), GVG, RFN
		GEFs+	Often not necessary	SCBs (CBZ, OXC, PHT, LGT)
		FS	Not indicated	-
	GoF	EIEE	Lack of data	-
SCN2A Nav1.2	GoF (onset< 3 months)	B(F)NIS, EIEE	SCBs (CBZ, OXC, PHT, LTG, MEX, LCS), KD	Unknown (GABAergic agents?)
	LoF (onset> 3 months)	Infantile/childhood DEE other DEEs	GABAergic agents (VPA, BZD, STP), CBD	SCBs
SCN8A Nav1.6	GoF	Severe DEE	SCBs (PHT, CBZ, OXC) at supra-therapeutic doses, BZD, KD	LEV
	GoF (rare partial LoF)	Intermediate DEE	SCBs (CBZ, LGT, PHT), VPA	(LEV)
	GoF / partial LoF	BFIS	SCBs (CBZ) self-limiting	-
SCN3A Nav1.3	GoF (developing brain)	EIEE	SCBs (LCS, PHT, CBZ)	Unknown
SCN1B β1 subunit	Partially understood: LoF / potentially deleterious GoF	GEFs+ DEE similar to DS	GABAergic agents (VPA, BZD, STP)	Unknown

Musto E, et al. Eur J Ped Neurol 2020;24:123-128

Avoid sodium channel blocker in DS

- CBZ, OXC, PHT, LTG, VGB



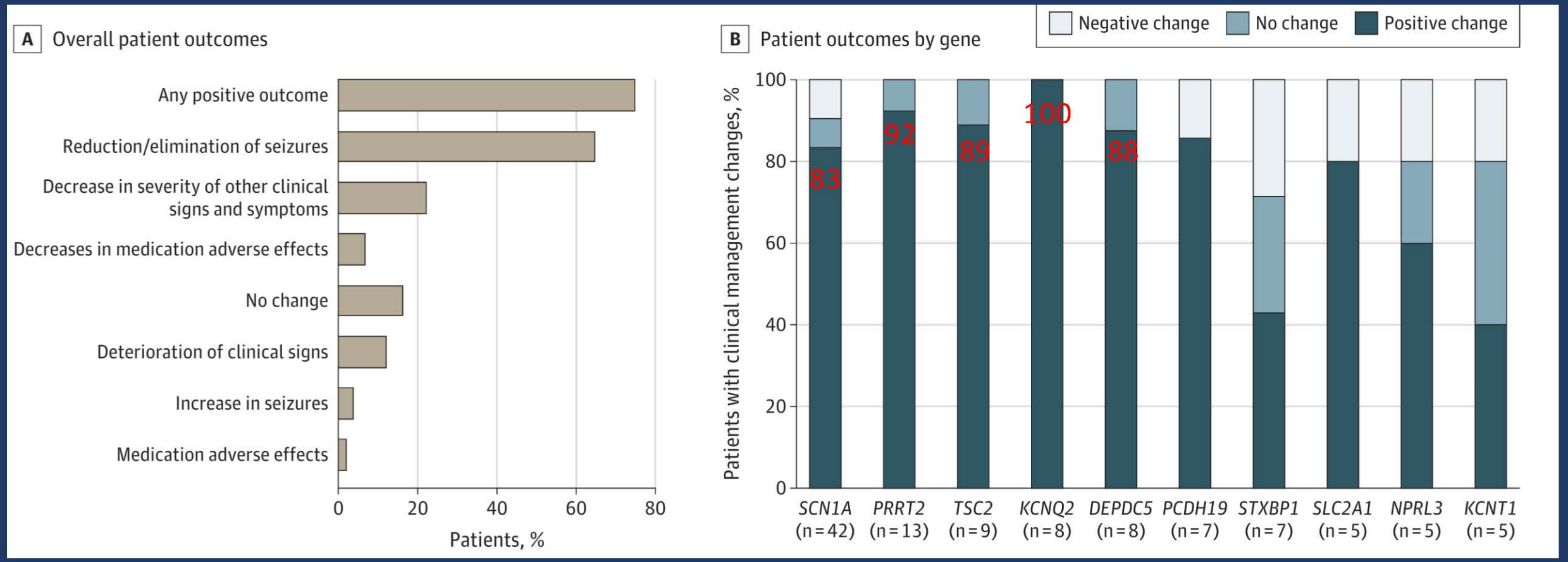
- Negative impact on cognitive outcomes if longer use of contraindicated ASMs in Dravet syndrome

de Lange IM, et al. Epilepsia 2018

Influence on treatment management

- 208/418 (50%) led to changed clinical management
  - Most common changes in *TSC2, SCN1A, MECP2, PCDH19, KCNQ2*
    - Adding new medication
    - Initiating medication
    - Refer to specialist
    - Monitor extra-neurological disease
    - Stop medication
- 125/167 (75%) associated with improved outcome (seizure reduction and seizure free)
  - 108/167 (65%): seizure reduction or seizure free

McKnight D, et al. JAMA Neurol 2022;79:1267-76



McKnight D, et al. JAMA Neurol 2022;79:1267-76

Impact on treatment

- Offered to patients with epilepsies with unknown causes
- Treatment impact: 45%
  - 36% Change in ASM
  - 7% Disease specific vitamin/metabolic
  - 3% Pathway-driven off-label
  - 10% Gene specific trial
- At least one category in 72%
  - 34% more than 1
- Care coordination 48%
- Counseling or change in prognosis 28%
- Correction of diagnosis 1.3%

TABLE 4.
Impact of Genetic Diagnosis on Individual Medical Management for 152 Individuals With Infantile or Childhood-Onset Epilepsy

Type of Impact on Medical Management	n (%) of 152 Individuals With Genetic Diagnosis	Case Examples
Impact in any category	110 (72.4)	
Impact in more than one category	51 (33.6)	
Treatment impact	69 (45.4)	
Choice of antiseizure medications	54 (35.5)	• Treatment with lacosamide (sodium channel blocker) in an individual with a gain-of-function *SCN8A* variant • Treatment with oxcarbazepine in an individual with a *PRRT2* variant with benign familial infantile seizures, with excellent response • Avoidance of sodium channel blockers in an individual with a loss-of-function *SCN2A* variant
Vitamin or metabolic treatments, gene-specific (including ketogenic diet)	10 (6.6)	• Treatment with pyridoxal-5′-phosphate in an individual with a homozygous *PNPO* variant • Treatment with ketogenic diet in individual with glucose transporter disorder (an *SCL2A1* variant) • Treatment with a mitochondrial cocktail in an individual with *POLG* variants
Pathway-driven off-label use of medications	5 (3.3)	• Treatment with memantine in an individual with a *GRIN2A* gain-of-function variant[17] • Discussion of treatment with quinidine in an individual with a *KCNT1* variant • Treatment with riluzole in an individual with an *SCN2A* gain-of-function variant
Disease/gene-specific clinical trials or IND use	15 (9.9)	• Consideration of enrollment in ganaxolone clinical trial for an individual with a *PCDH19* variant and another individual with a *CDKL5* variant • Enrollment in a fenfluramine trial for an individual with an *SCN1A* variant
Care coordination (medical management and monitoring for disease-associated features)	73 (48.0)	• Request for renal ultrasound for an individual with Koolen-de Vries syndrome (*KANSL1* variant) • Referral to multiple specialists for an individual with Mowat-Wilson syndrome (*ZEB2* variant) • Request for EKG and cardiology evaluation for individual with an *SCN1B* variant
Change in prognosis	42 (27.6)	• Counseling on risk of early lethality in an individual with a *BRAT1* variant[48] • Discussion of benign prognosis with future possibility of seizure freedom in an individual with a *PRRT2* variant • Counseling on prognosis in an individual with *NHLRC1* compound heterozygous variant-related Lafora disease
Correction of diagnosis, for those with a diagnosis before genetic testing	2 (1.3)	• Clarification of diagnosis for an individual with a *CACNA1A* variant and another individual with a *GNAO1* variant, both previously considered to have primary mitochondrial disorders

Abbreviations:

Haviland I, et al. Ped Neurol 2023’138:71-80

What we/patients get from the test?

- Accurate Diagnosis
- Personalized Treatment Plans
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Sheidley BR, et al. Epilepsia 2022;63:375-387

Etiology-based

Etiology-based	Gene	Treatment
Preventive	TSC1/TSC2	Vigabatrin prior to seizure onset
	ALDHT7A1	Maternal administration of B6
Clinical trial	*SCN1A*	ASO/STK-001
	Nonsense *SCN1A*	Ataluren
	CDKL5 deficiency	Ataluren

Marini C, Giardino M. Br J Clin Pharmacol 2022;88:2539-2551

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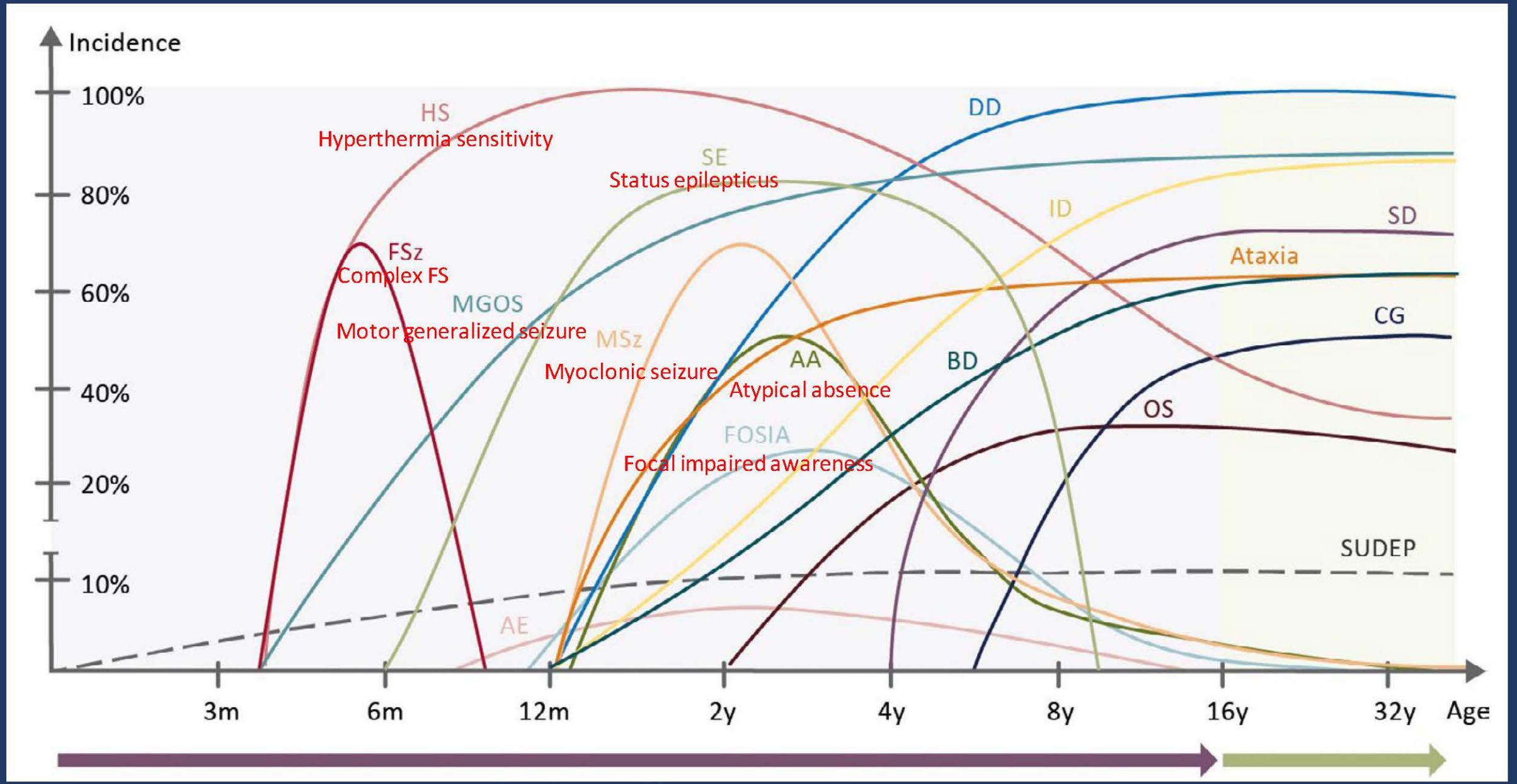
Sheidley BR, et al. Epilepsia 2022;63:375-387



Cardenal-Munoz E, et al. Epilepsia Open 2022;7:11-26

What we/patients get from the test?

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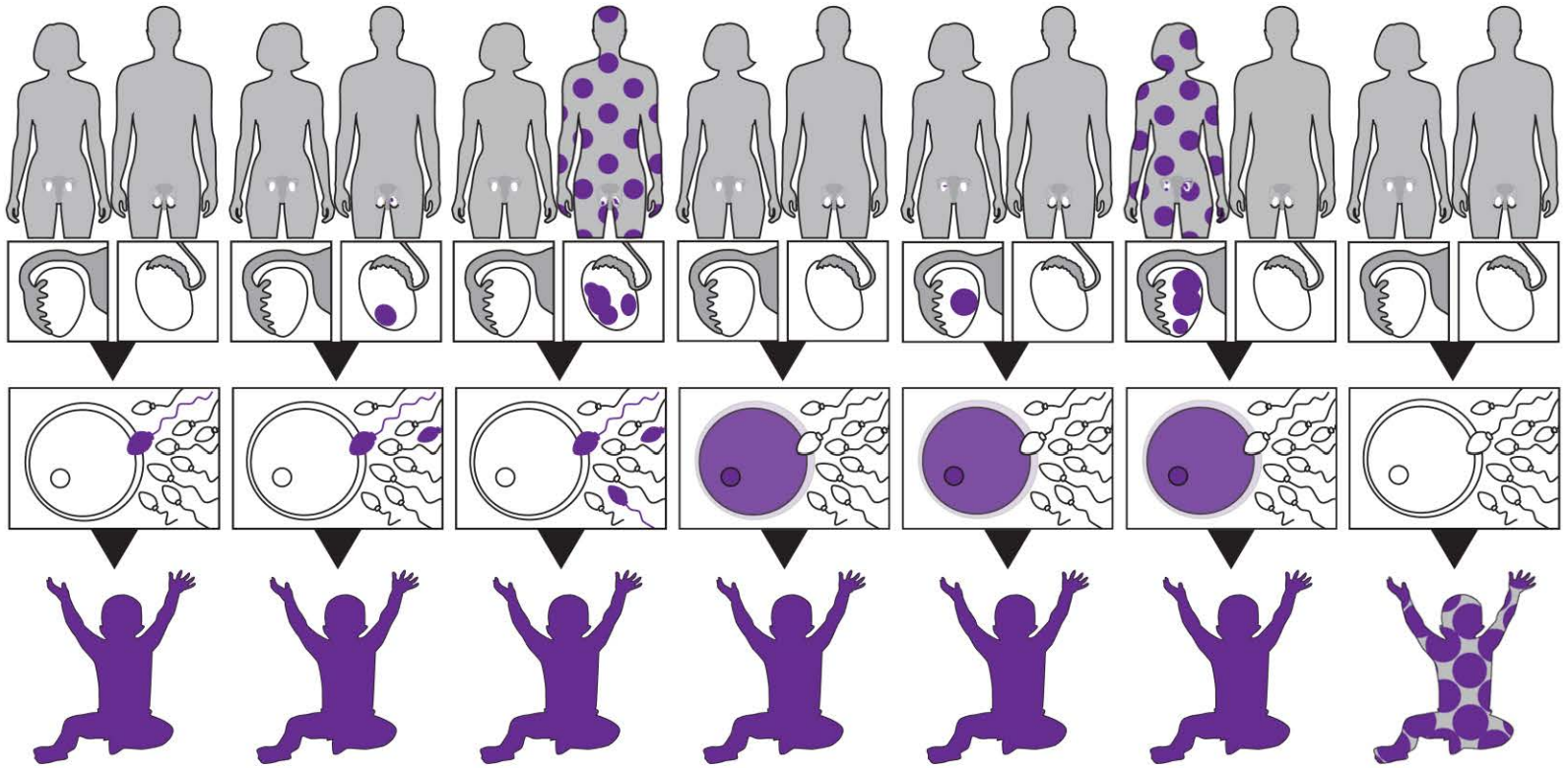
- Prognosis
- Risk Assessment for Family Members
  - AD
  - AR
  - X-linked
  - Mitochondrial
  - De novo mutation
    - Recurrence rate 1-2%
    - Complicate issues

Sheidley BR, et al. Epilepsia 2022;63:375-387



category	A	B	C	D	E	F	G
mutation type	paternal one-off mutation	paternal gonadal mosaicism	paternal mixed mosaicism	maternal one-off mutation	maternal gonadal mosaicism	maternal mixed mosaicism	post-zygotic mutation in child
proportion of cases from literature	71%	2%	2%	15%	2%	2%	6%
recurrence risk (to another child)	negligible	1-50%	1-50%	negligible	1-50%	1-50%	0%
risk quantifiable?	yes	yes	yes	no	no	no	yes

Bernkopt M, et al. 2023;14:853

Why do we need genetic tests in epilepsy

- What we/patients get from the test?
- Whom to test?
- Pre-counseling needed?
- Which genetic tests?

Whom to test?

- Unexplained epilepsies
- Epileptic encephalopathies
  - 90% of currently known epilepsy gene are patients with DEE
  - Abnormal genes can be found in 30-40% of cases in addition to 5-10% found by CMA
- Epilepsy plus
  - Associated with ID, ASD, GDD, dysmorphic features, systemic malformation
- DRE of unknown etiologies
- Familial epilepsies

Smith L, et al. J Genet Couns. 2023;32:266–280
Fonkeu Y, Ellis CA. Practical neurology 2023
Sheidley BR, et al. 2022;63:375-387
Krey I, et al. Epileptic Disord 2022;24:765-786

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Genetic counseling

- Informed consent
  - Understand the ramification of the test Pretest and post-test genetic counseling
  - Weigh risk and benefit of the test
    - Insurance, social stigma, family dynamics
  - Limitation of the test and consequences
    - Positive : any benefits (precision medicine) or changes in treatment or nothing
      : comorbidities and surveillance
      : family planning
    - Negative or even more stressful : variant of unknown significant
  - Other issues
    - variants of unclear significance
    - paternity
    - discover of gene not related to diseases

Smith L, et al. J Genet Couns. 2023;32:266–280
Ottman R, et al. Epilepsia 2010;51 (suppl 5)

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Which genetic test

- Genetic test should be guided by clinical phenotypes which will have affect on
  - Should or should not have genetic test
  - Testing approach (which tests should be ordered)
  - Interpretation

Genetic test

- Chromosome Karyotype
- Chromosome microarray
- Biochemical studies
- Single gene sequence
- Gene panels
- Whole exome sequencing
- Whole genome sequencing

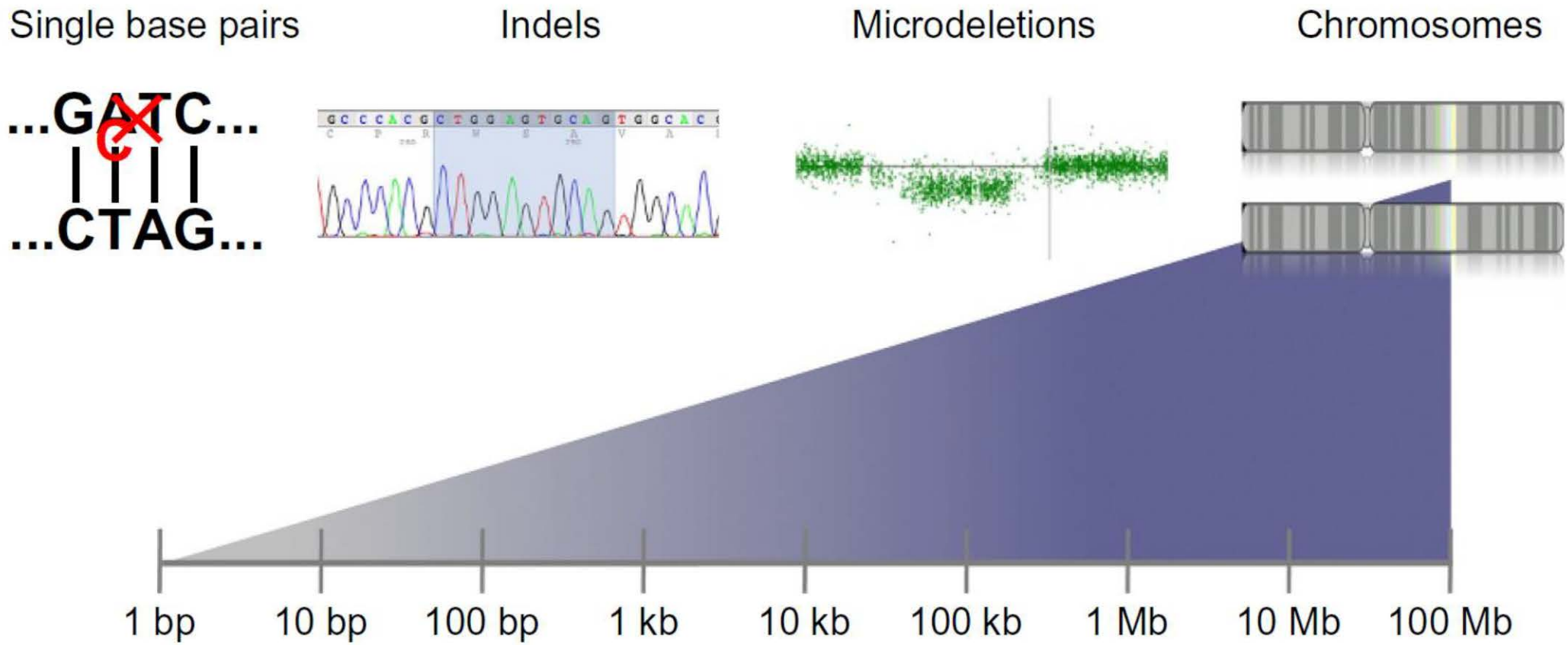
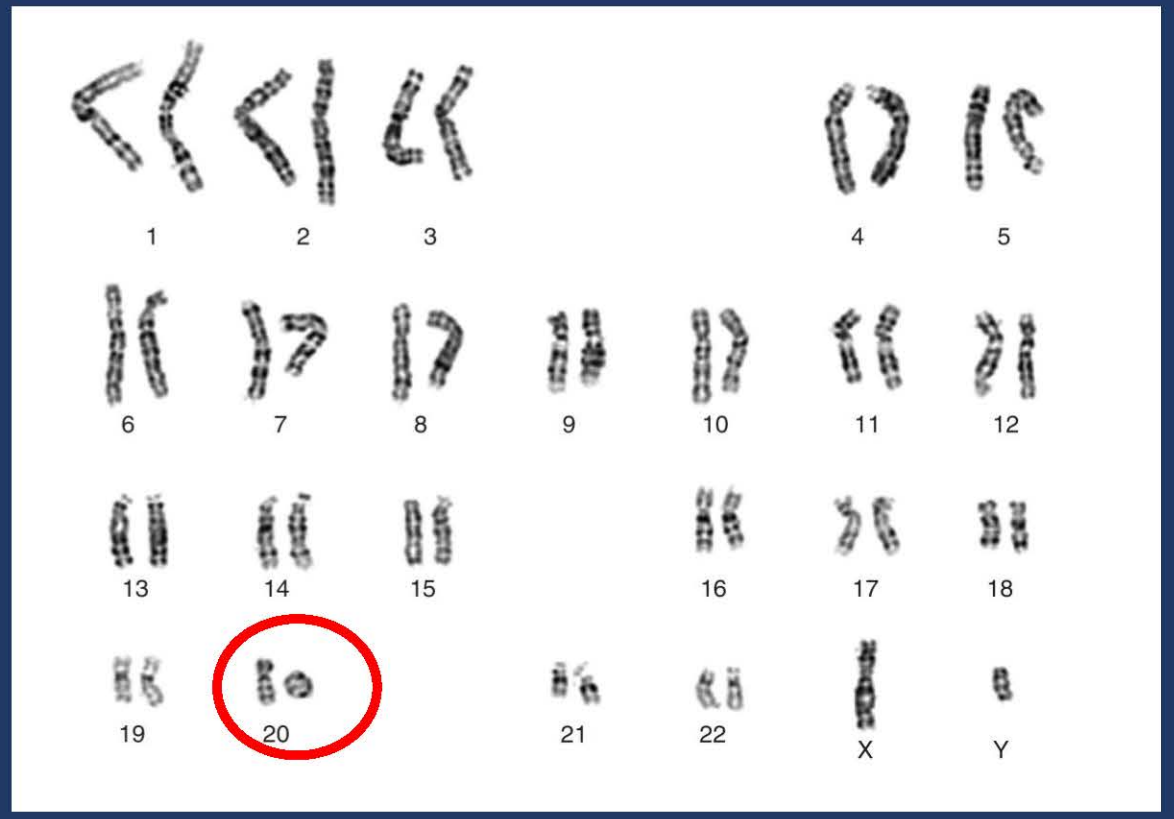


FIGURE 1

The range of genetic variants predisposing to human disease by size.

Helbig I. Progress in Brain Research 2014

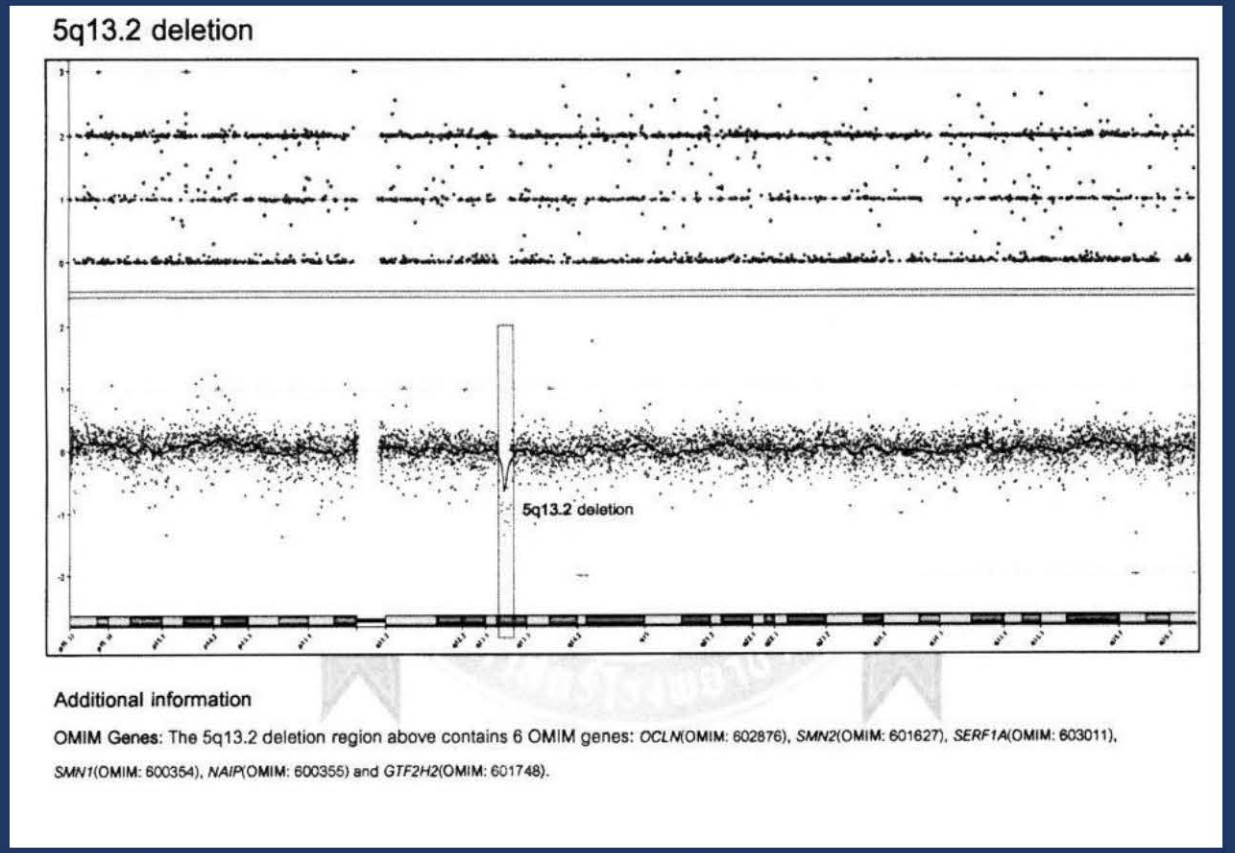
Chromosome Karyotype



- Detect aneuploidy, translocation, inversion, large deletion/duplication
- Identify mosaicism
- Poor for point mutation, microdeletion/duplication
- **Minimal role in epilepsy**
- Except for Ring chromosome 20

Alpman A, et al. Dev Med Child Neurol 2005;47:343-46

Chromosome microarray

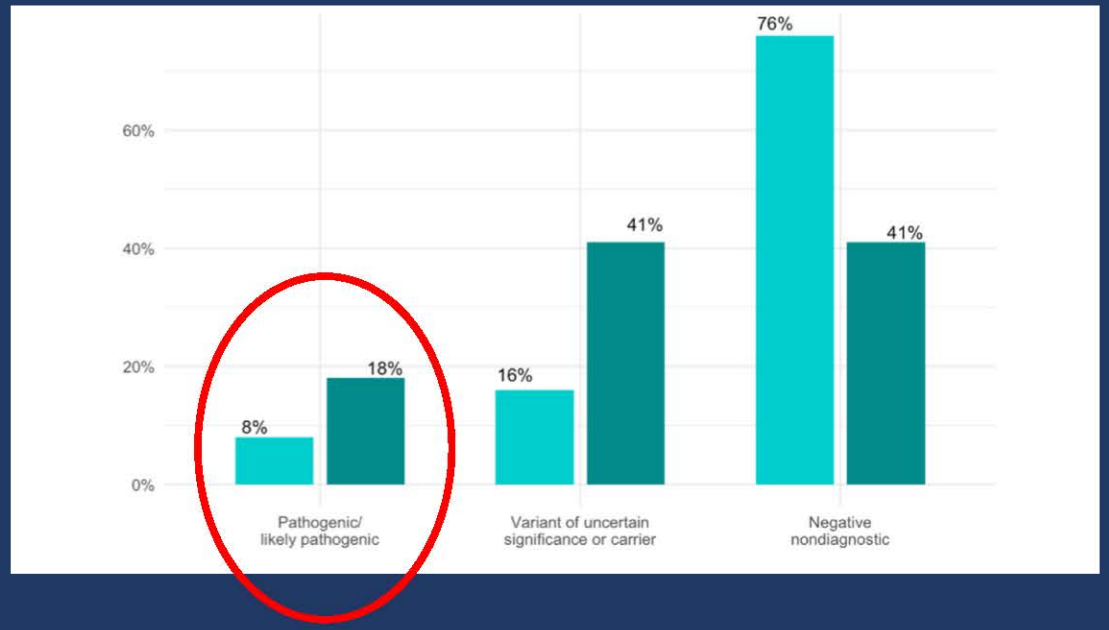


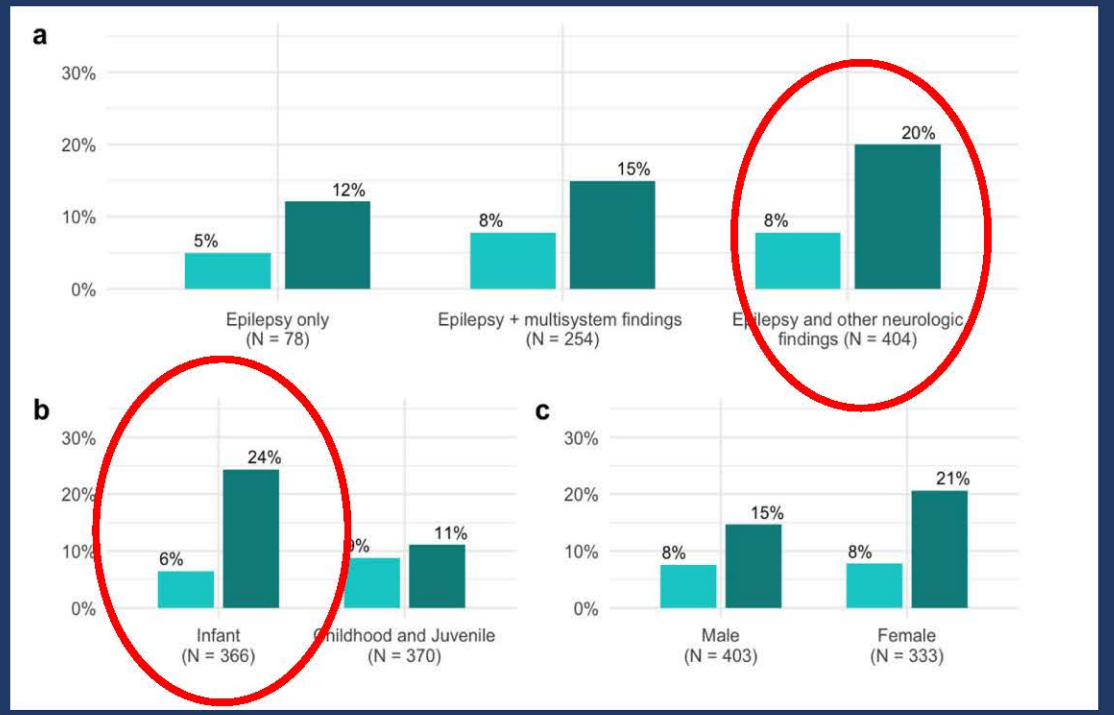
- Detect CNV
- Microdeletion/duplication
  - Not for balanced translocation/inversion
  - Not for point mutation
- Yield is between 5-10%
  - Less than MGP
- May first indicate in patients with
  - GDD
  - ID
  - Multiple congenital malformation
  - Autistic spectrum disorders

Carter MT, et al. J Med Genet 2023;60:523-532

CMA and EGS in pediatric epilepsy

- 736 samples
  - 366 with CMA, 370 EGS: 114 with both

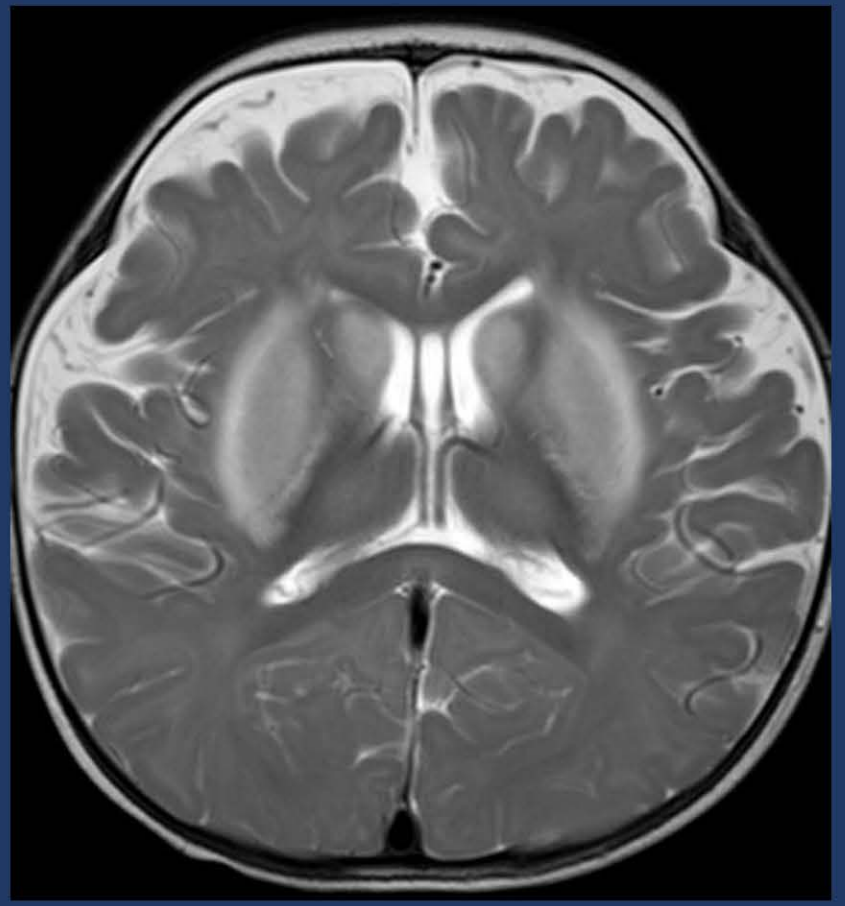




Burk KC, et al. Ped Neurol 2024;150:50-56

Biochemical studies

- History of in utero seizures
- Myoclonic epilepsies in infant
- Infantile spasm
- Atypical absence
- Recurrent metabolic de-compensation
- EEG: burst suppression
- MRI with metabolic pattern

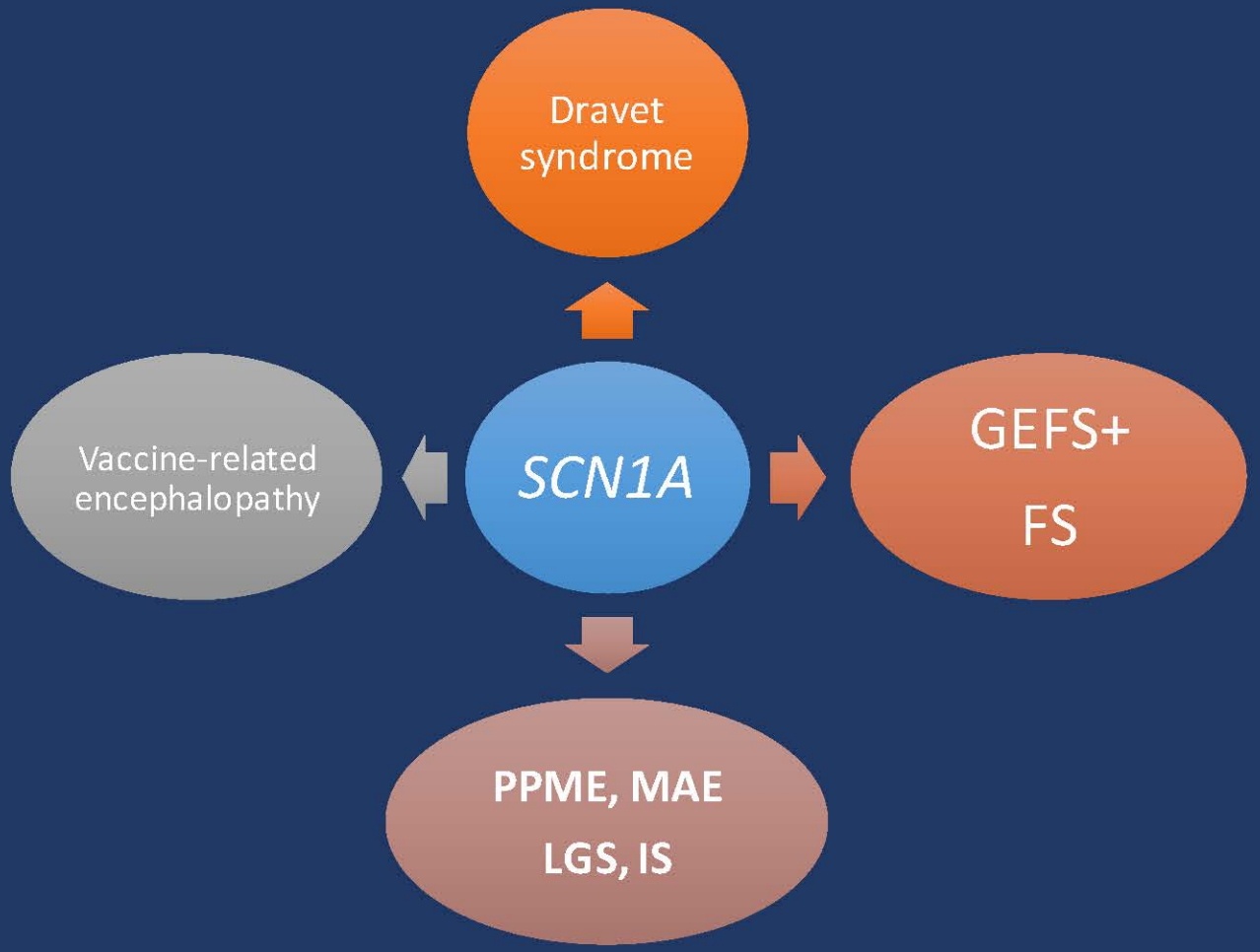


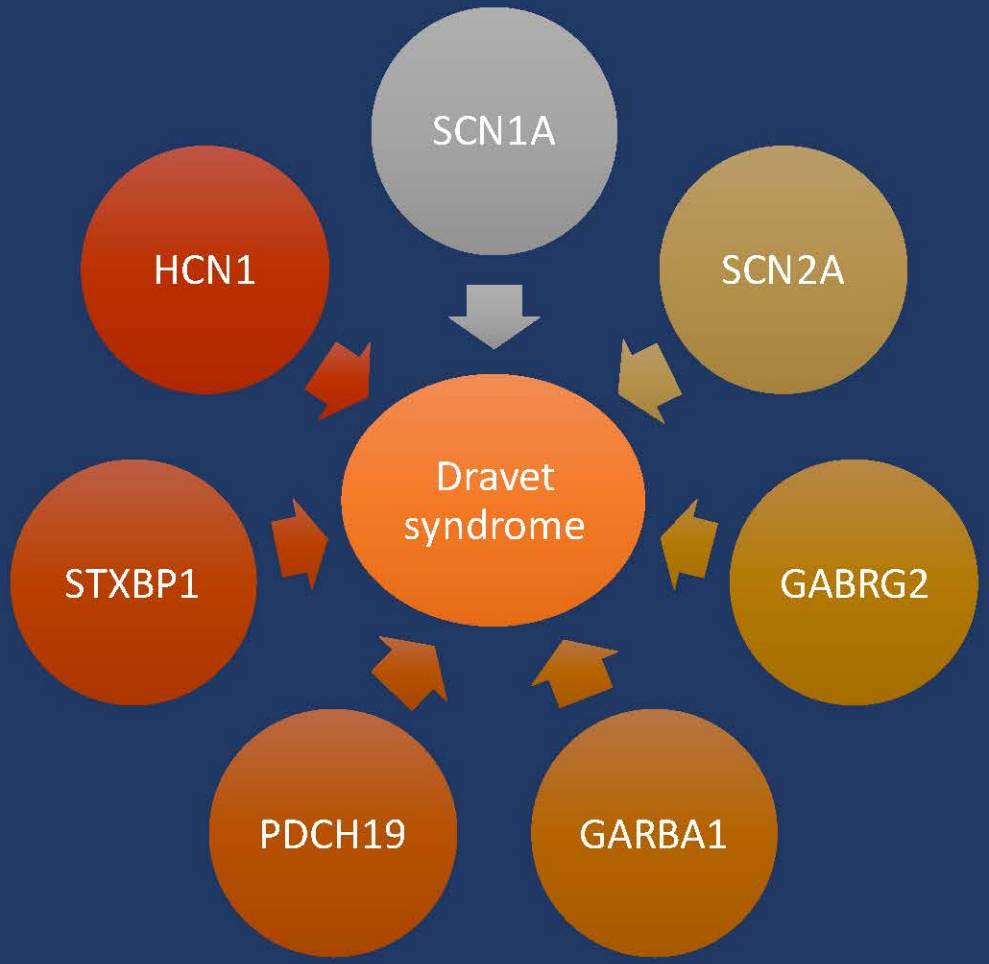
Ream MA, et al. Epilepsia 2015

Targeted single gene sequence

- Single targeted gene is sequenced
- It is used when certain clinical features point to suspected candidate gene
- Dravet syndrome
  - 80% of cases with *SCN1A* mutation

Clinical Heterogeneity
(One gene causes more than one phenotype)





Genetic Heterogeneity

(One phenotype causes by many genes)

Genetic heterogeneity

Epileptic syndrome	Gene or genetic causes
BFNS	KCNQ2, KCNQ3
EIEE	ARX, CDKL5, SLC25A22, STXBP1, SPTAN1, SCN1A,…
EME	SLC25A22, Inherited metabolic disorders (NKH, ..)
EIMFS	KCNT1, SCN1A,…
WS	ARX, CDKL5, other chromosome/single gene
GEFC+	SCN1B, SCN1A, GABRG2, SCN9A
DS	SCN1A, GABRG2, SCN1B, SCN2A, PCDH19,..

Clinical heterogeneity

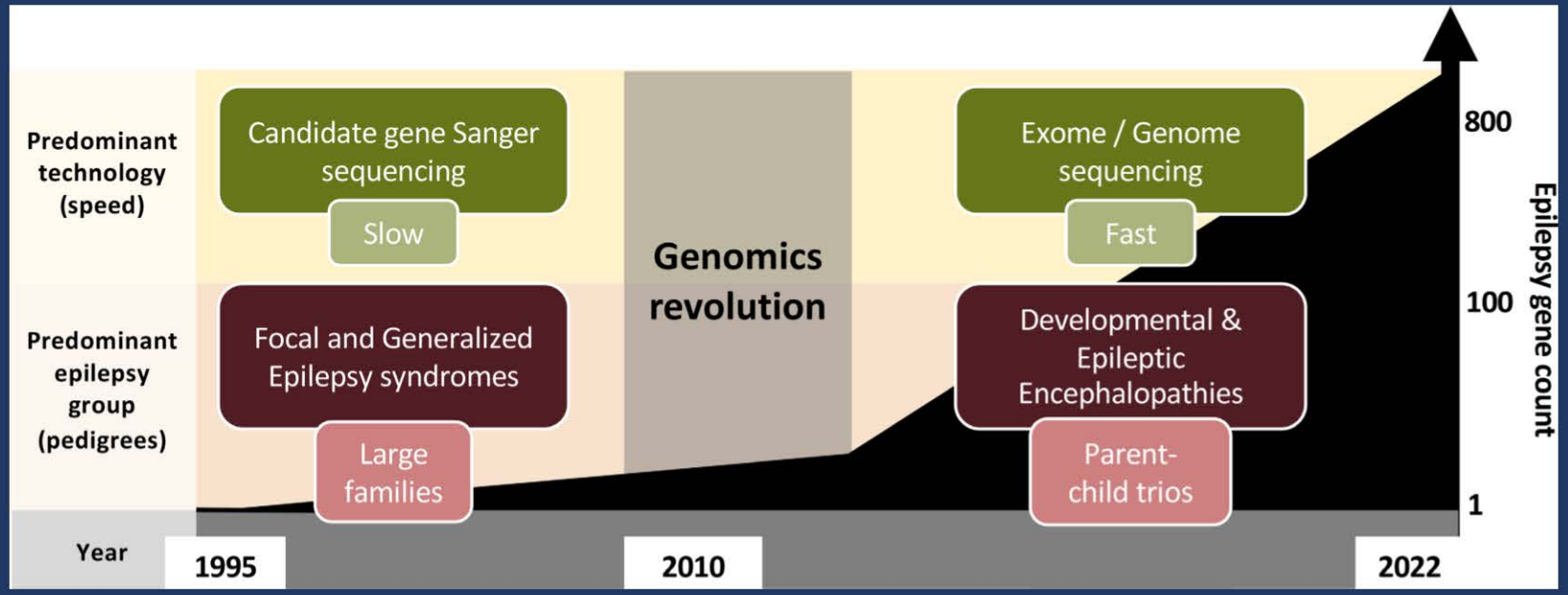
Gene	Epileptic syndrome
SCN1A	DS, GEFS+, predispose to FC, Doose, LGS,
SCN1B	GEFS+, DS
SCN2A	BFNIS, IS, EIEE
GABRG2	DS, Doose, GEFS+
PDCH19	DS, LGS, Infantile or early childhood onset female
ARX	Male with XL-IS, WS, EIEE, Lissencephaly, ID

Limitation of single gene sequence

- There are limits to clinical features as
- Similar clinical features can be caused by different genes (Genetic heterogeneity)
- The same gene gives rise to ranges of phenotypes (Clinical heterogeneity)

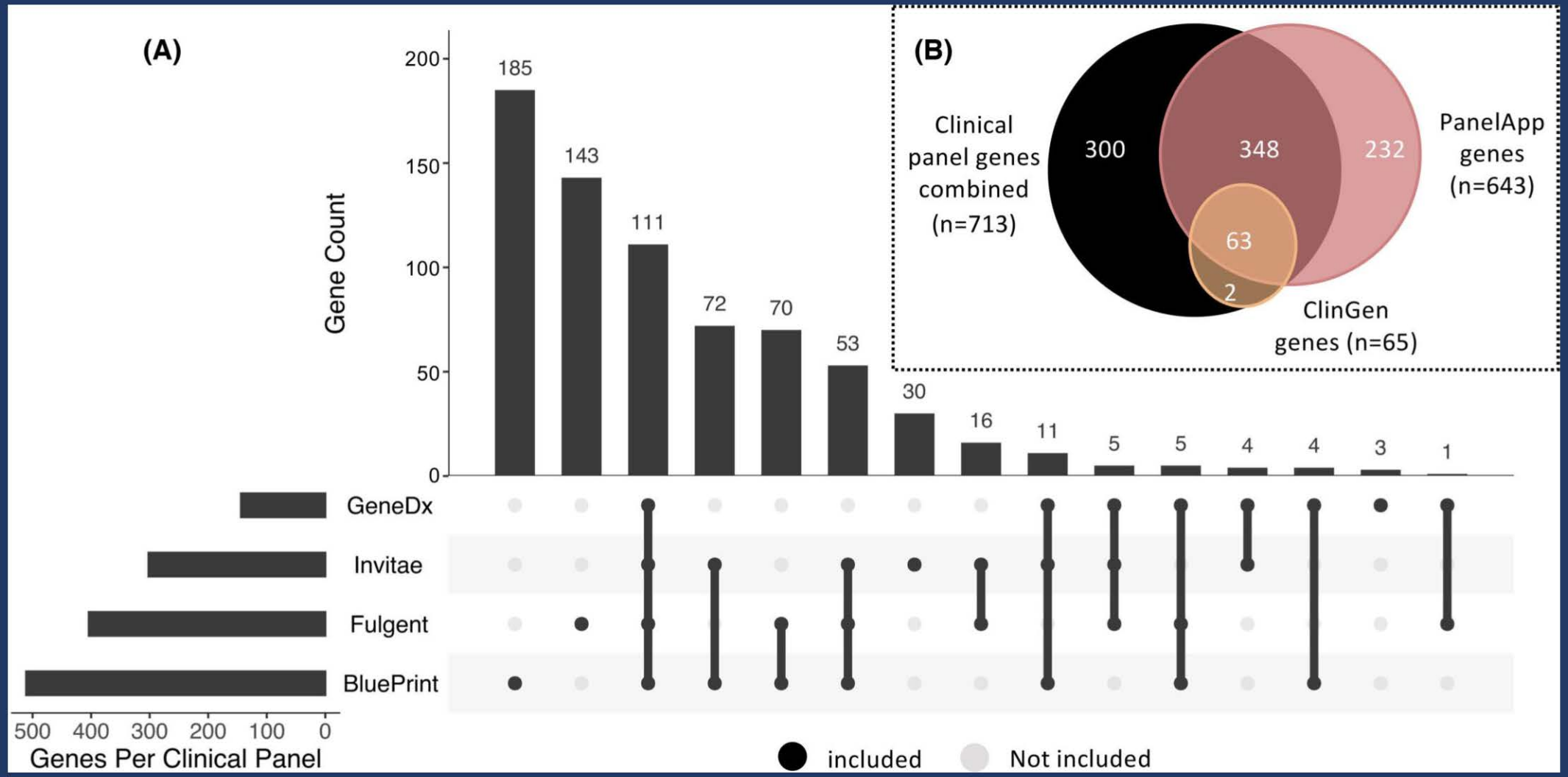
How many epilepsy genes are there?

- First established gene is *CHRNA4* in 1995
- More than 1000 genes are found to be associated with epilepsy with the discovery of WES/WGS
- Most epilepsy genes (90%) are associated with DEE phenotype



Oliver KL, et al. Epilepsia. 2023;64:1368–1375

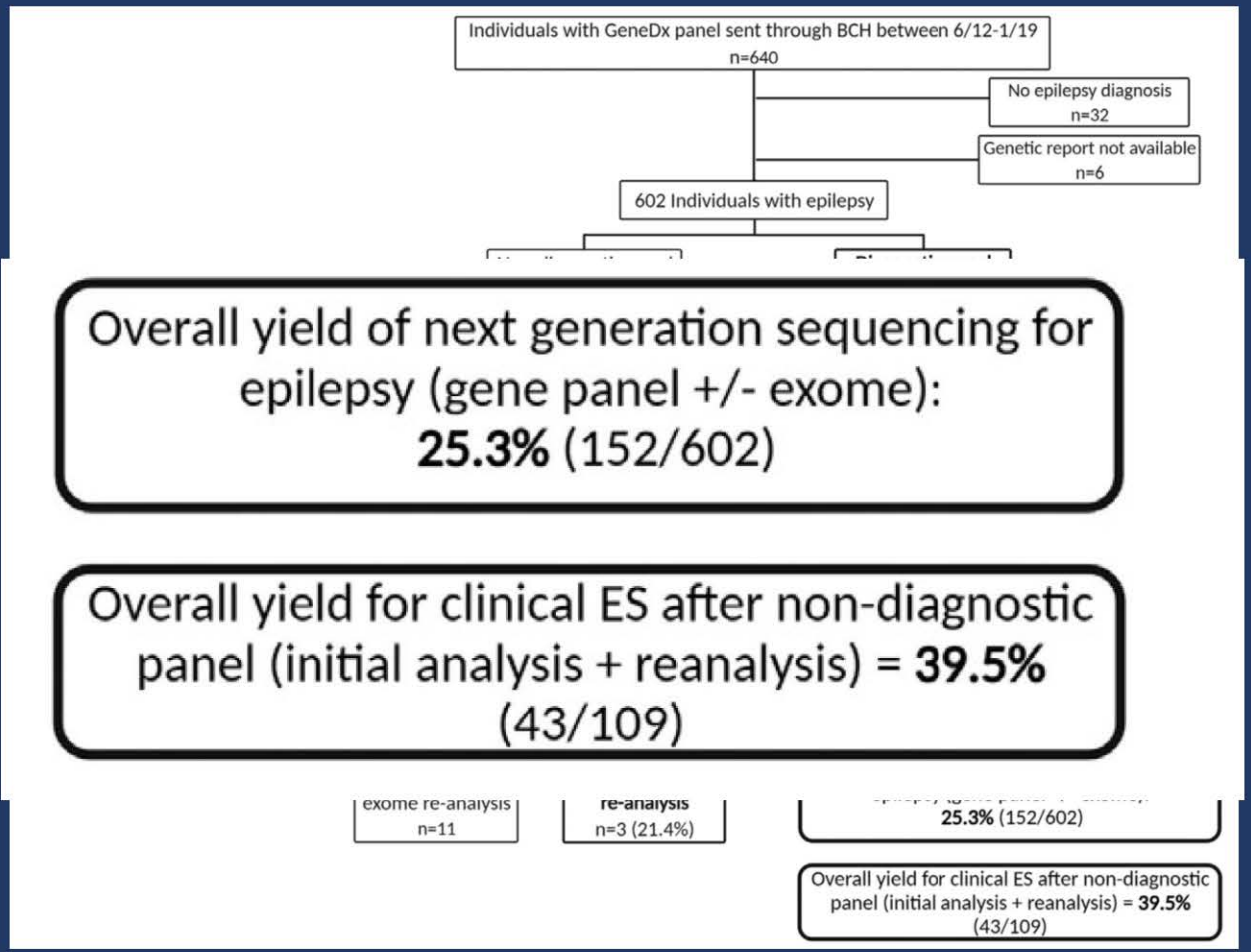
Difference in gene panel

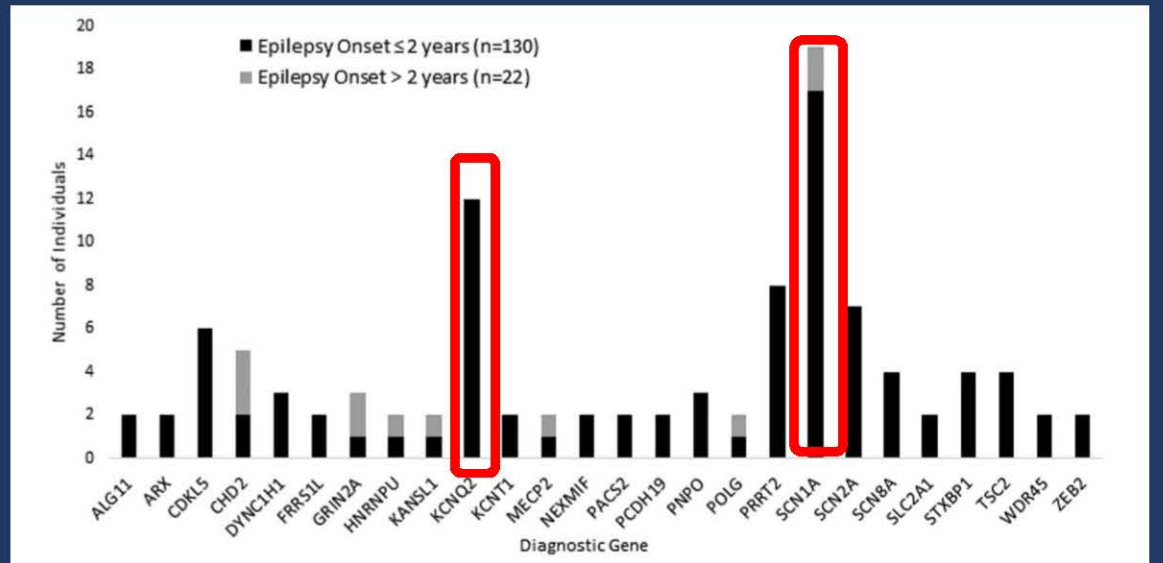


Oliver KL, et al. Epilepsia. 2023;64:1368–1375

Genetic diagnosis

- Offered to patients with epilepsies with unknown causes



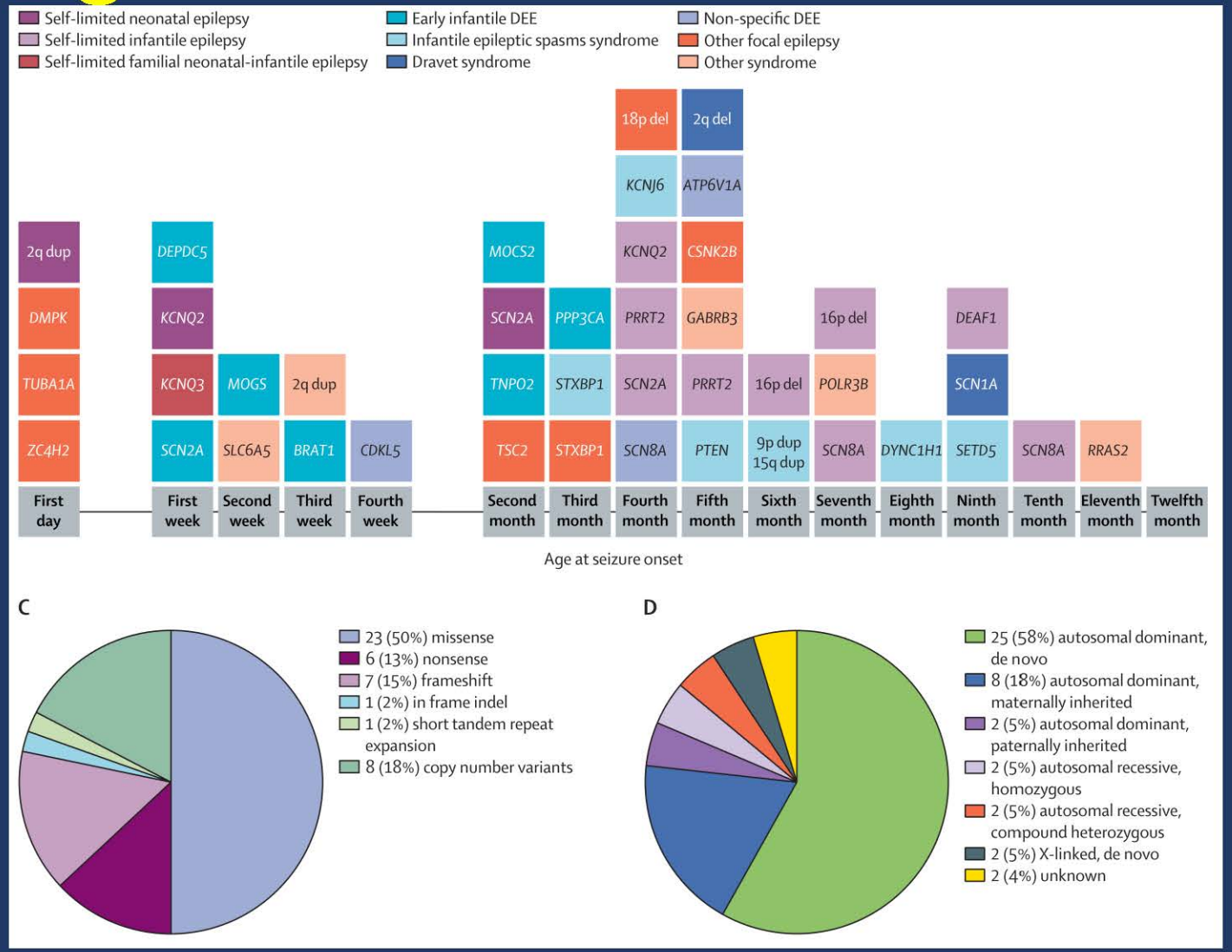


Additional genes for which variant(s) associated with epilepsy were identified, epilepsy onset ≤ 2 years (n=1 each)									
ACTB	*AGO1*	*AP4S1*	*ARHGEF9*	*ATP1A3*	*ATP6V1A*	*BRAT1*	*CACNA1A*	*CACNA1E*	*CHAT*
CNTNAP2	*COL4A1*	*DLL1*	*ERCC5*	*FOXG1*	*GABRB2*	*GABRG2*	*GNAO1*	*IFIH1*	*IQSEC2*
ITPA	*KCNH1*	*NRXN1/2*	*PLPBP*	*RHOBTB2*	*SCN1B*	*SEPSECS*	*SLC12A5*	*SPTAN1*	*TBL1XR1*
TRIM8	*TUBB2A*	*UBE3A*	*UPF3B*	*WDR73*					

Haviland I, et al. Ped Neurol 2023'138:71-80

Rapid genome sequencing

- Younger than 12 mo. at seizure onset
- New onset seizure, epilepsies, complex FC
- Exclude SFS, ASS, acquired cause or known genetic
- Yield 43%



D'Gama AM, et al. Lancet Neurol 2023;22:812-25

Diagnostic yield

- Systematic evidence review, 154 articles (39094 patients), published till 2020
- Overall diagnostic yield: 17%
  - GS: 48%
  - ES: 24%
  - MGP: 19%
  - CGH/CMA 9%
- Increase yield
  - 1. presence of developmental and epileptic encephalopathy and/or
  - 2. presence of neurodevelopmental comorbidities

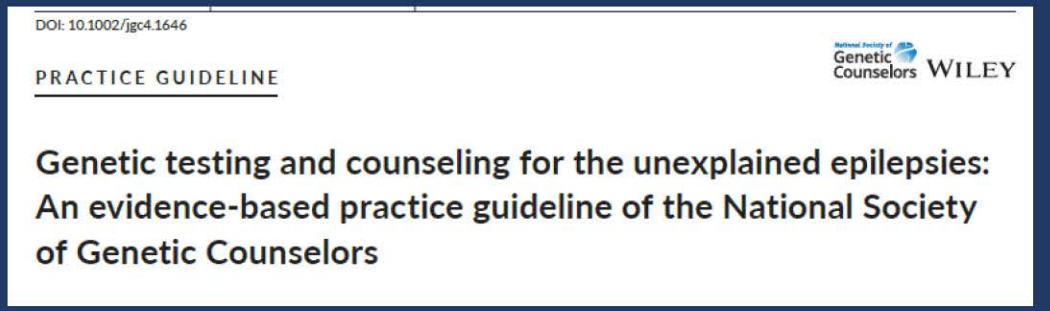
- Some studies included those who had negative MGP
- thus result of ES may be higher

Sheildly BR, et al. Epilepsia 2022;63:375-387

Testing method	Diagnostic yield in epilepsy
ES/Trio ES	Up to 45% [68]
GS/Trio GS	Up to 48% [19]
Epilepsy-based gene panels	Up to 25% [68]
Chromosomal microarray	5-15% [33, 34]
Sanger sequencing	Very low, nearly obsolete
Chromosome analysis	Very low

Krey I, et al. Epileptic disord. 2022;24:765-786

Genetic testing in epilepsy


DOI: 10.1002/jgc4.1646

PRACTICE GUIDELINE

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

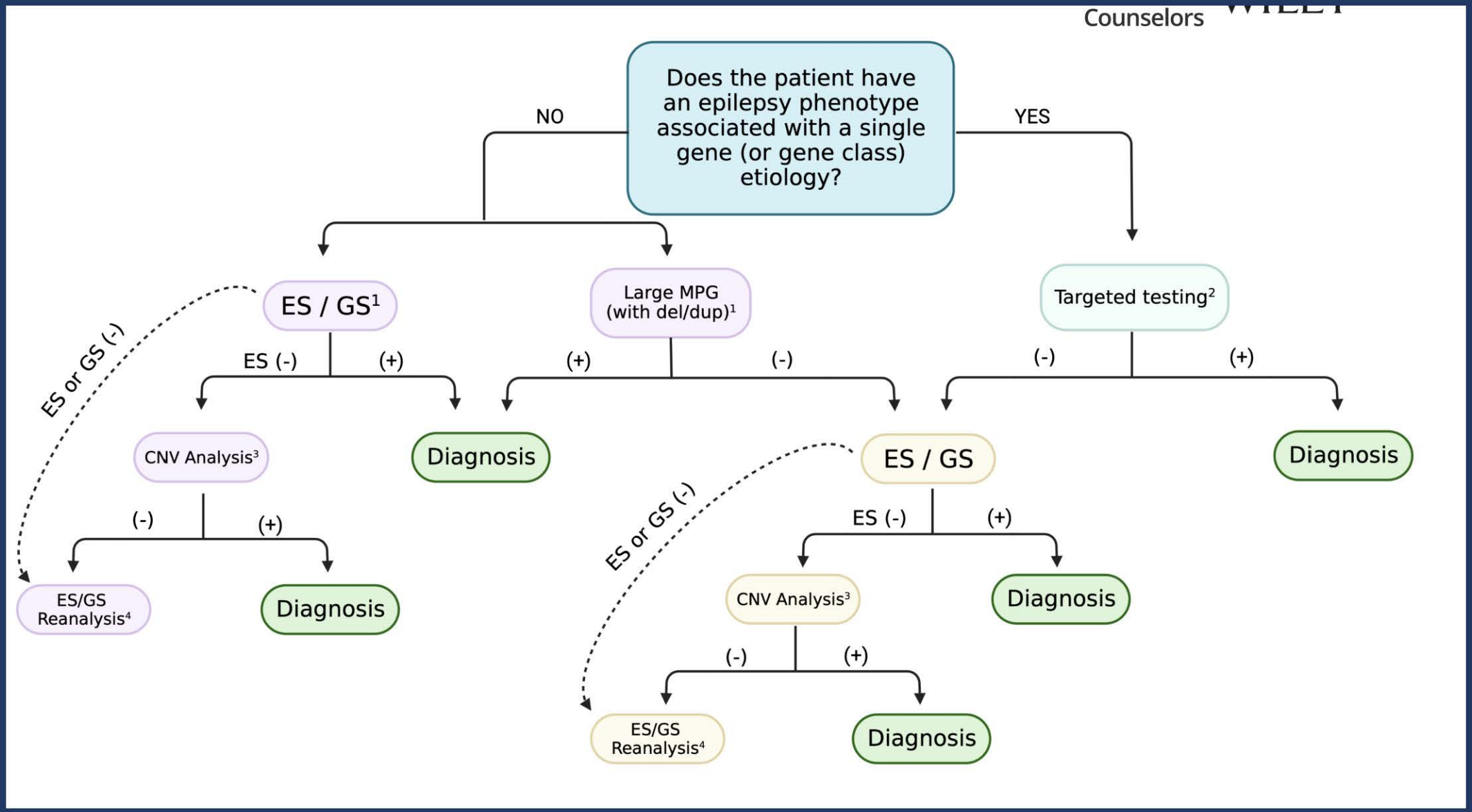
- Genetic cause is the main etiology of unexplained epilepsy
- Genetic testing becomes a major role in diagnostic tools in epilepsy management
- Now it is integrated in part of management
  - At least multi-gene panel is recommended
  - Exome and genome sequencing has more advantages
    - Genetic heterogeneity and rapid rate of gene discovery
    - Limitation in deletion/duplication and repeat expansions

Smith L, et al. J Genet Couns 2022;32:266-280

Testing modalities

	Genetic test			
	CGH/CMA	MGP	ES	GS
Variant detection				
Single nucleotide variants (coding region)	–	+	+	+
Single vucleotide variants (non-coding region)	–	(–)	(–)	+
Nucleotide Repeats	–	Δ	–	Δ
Single Exon CNV	Δ	(+)	–	+
Multi Exon CNV	+	(+)	Δ	+
Full Gene CNV	+	(+)	Δ	+
Multi Gene CNV	+	–	Δ	+
Structural Rearrangements	–	–	–	+
Methodology				
Targeted gene list	–	+	–	–
Potential for variants in novel/candidate genes	+	+	+	+
Concurrent, trio-based analysis standard	–	–	+	+

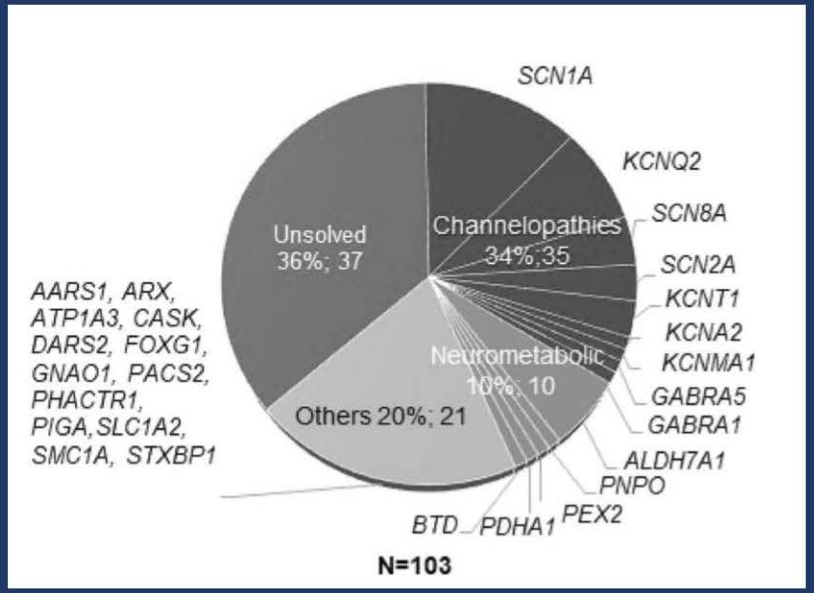
Smith L, et al. J Genet Couns 2022;32:266-280



Smith L, et al. J Genet Couns 2022;32:266-280

Thai study

- Dravet syndrome
  - Single gene study
  - 14/20 with pathogenic *SCN1A*
    - 6 novel mutations
  - 1 with *PDCH19*
- Infantile onset (<12 mo.) and DRE
  - Diagnostic yield 64% (ES-62% + GS-2%)
  - 66 pathogenic and likely pathogenic SNV in 27gene



Virawan S, et al. JSHMR 2022;40:301-308
Boonsimma P, et al. Eur J Human Genetics 2023;31:179-187

Practice guideline

- Difference in each countries
- Based on
  - Epidemiology
    - May different in each countries
  - Cost-effectiveness
  - Economy
  - Impact of treatment
    - Availability of treatment
    - Opportunities in research

Smith L, et al. J Genet Couns 2022;32:266-280

Practical guideline

- Accurate clinical history, physical examination, EEG
- CLUES in diagnosis
- Select appropriate, cost-effective and helpful diagnostic tests

Genetic test	Recommended Use	Limitations	Notes	
Karyotype	Strong suspicion for ring chromosomal disorder	No SNV detection or small deletion/ duplication detection	In epilepsy cohorts, particularly relevant to assess for Ring 20 and Ring 14 related disorders.	
Chromosomal microarray	Consider for cases with multi-systemic phenotypic features, developmental delay, and/ or autism Microdeletion syndromes have been associated with isolated epilepsy presentations Clarification of unclear results from other testing	No single nucleotide variation (SNV) detection Deletions/duplications may now be detected in whole exome Lower diagnostic yield in children for whom epilepsy is the primary presenting symptom	Consider if WES and gene panel are negative Yield ~5%	
Single gene or single disorder testing	Methylation studies	Strong clinical suspicion for particular syndrome with negative prior testing	Not comprehensive, used to detect only particular disorders	In epilepsy cohorts, particularly relevant for assess for Angelman and Prader Willi Syndrome
	Fragile X testing	Standard of care in children with autism and developmental delay	Not comprehensive, used to detect only a particular disorder	
	Trinucleotide repeat disorders	Strong clinical suspicion for a particular disorder, particularly in patients with progressive disorders, with negative WES	Not comprehensive, used to detect only particular disorders	In epilepsy cohorts, particularly relevant to assess for *CSTB* (Unverricht-Lundborg) or *ARX* related conditions
Multigene panel	Epilepsy with unclear etiology, particularly if access to WES/ WGS is limited	Limited in scope compared to WES Gene panels vary widely in number and clinical validity of genes tested	Accessible for neurologists who may not have access to genetic counselors or a specialized center Include the most common epilepsy-related genes, testing between 100 and 300 genes Many labs allow for free parental testing if clinically relevant May yield more rapid results if rapid exome or genome is not available Yield ~10-20%	
Whole exome sequencing (with mitochondrial DNA)	Epilepsy with unclear etiology, with concomitant features of autism or developmental delay Negative prior testing (i.e multigene panel) with strong suspicion for underlying genetic disorder	May not pick up deep intronic variants May not pick up repeat expansion disorders Limited detection of larger copy number variation (CNVs; i.e. microdeletion and microduplication syndromes)	May send trio-based testing (i.e. test both parents in conjunction with proband to aid in variant interpretation) Allows for the detection of novel epilepsy genes in the setting of rapid gene discovery Yield ~20-25%. Up to 50% yield in children with early onset DEE	
Whole genome sequencing	Detection of deep intronic variants Detection of repeat expansions Detection of structural rearrangements leading to gene disruptions	Depth of sequencing is typically lower than WES, leading to some instances of SNVs in exons that are not detected Limited clinical availability outside of specialized centers		

Karlin A, et al. Curr Probl Pediatr Adoles Health Care in press

Karyotype and CMA

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Karlin A, et al. Curr Probl Pediatr Adoles Health Care in press

Single gene, MGP, WES

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Karlin A, et al. Curr Probl Pediatr Adoles Health Care in press

Summary

- Genetic testing has an important role in management of epilepsy of unknown etiology
- Correct diagnosis has huge impact on several aspects
- For now, at least multiple gene panel should be the first test
- However, this should be individualized based on clinical diagnosis
- Now in Thailand, practice guideline is now in the process