ROMA

17-18 marzo 2026

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5th edition

next generation in neurologia

UNIVERSITÀ DEGLI STUDI DI GENOVA

GASLINI

EpiCARE

La rivoluzione genetica in epilessia

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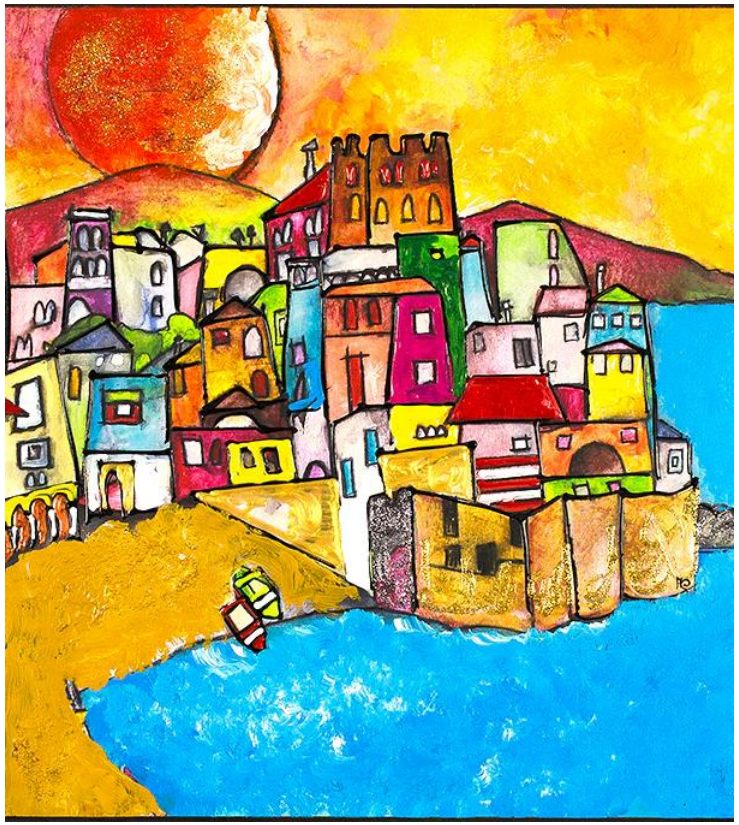
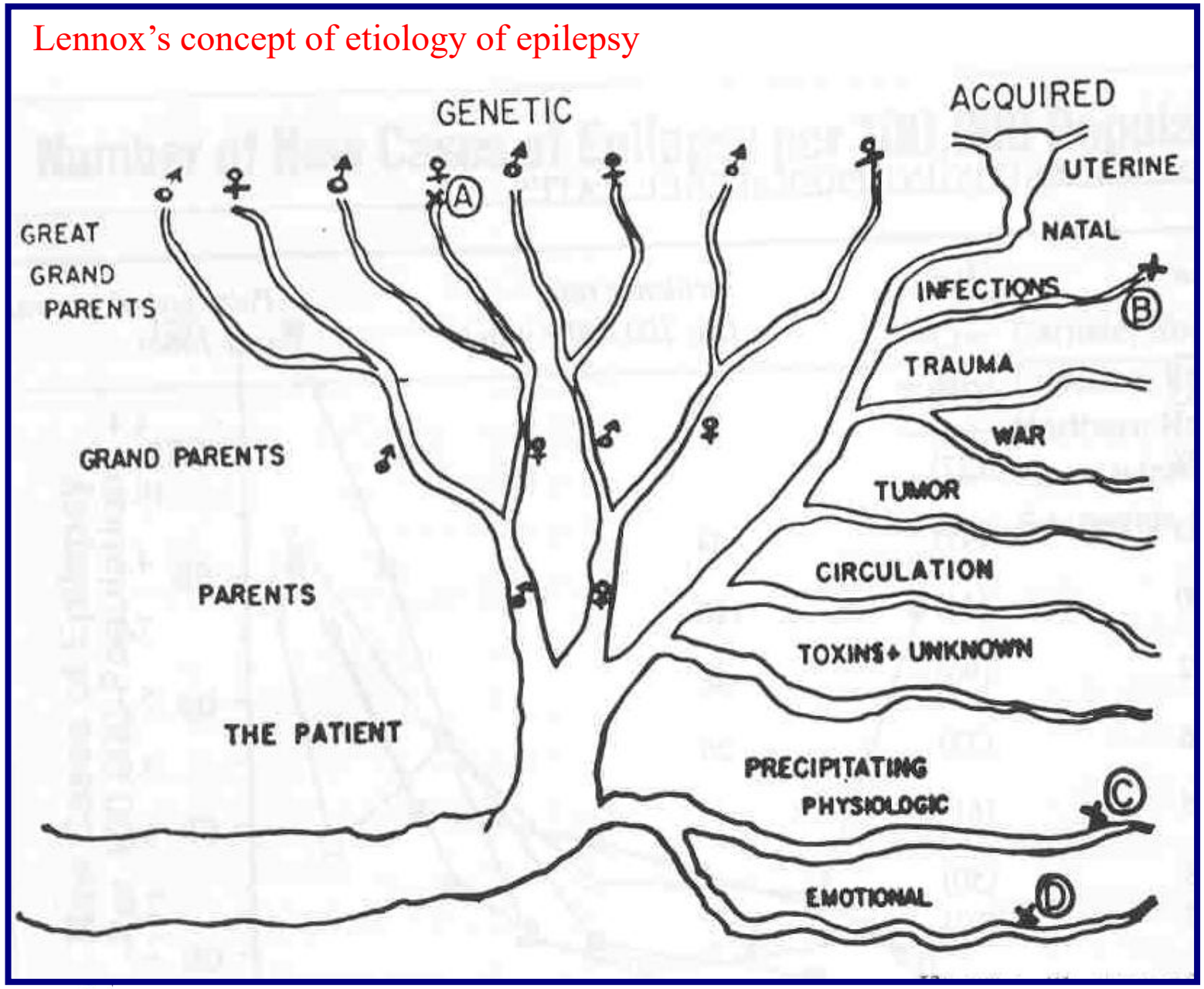
Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genova, Genova



Disclosures

- Received honoraria from Jazz Pharmaceuticals, UCB Pharma, STOKE Therapeutics, BIOCODEX and Proveca Pharma Ltd
- The scientific contents reported are independent of commercial economic interests

Lennox's concept of etiology of epilepsy



Lennox & Lennox, Epilepsy and related disorders, 1960 Little Brown, Boston, vol I, p. 529

See also: Shorvon. Causes of Epilepsy, Cambridge University Press, 2011

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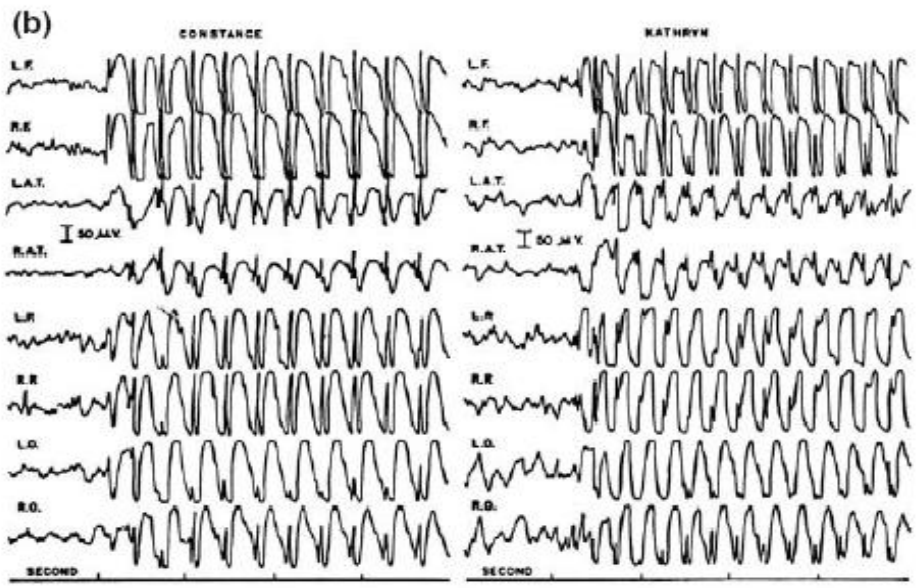
Epilepsy in twins

Lennox's series (1960)

(c)

	Casewise concordance	
	Monozygous twins	Dizygous twins
Generalized epilepsies	0.81	0.26
Focal epilepsies	0.36	0.05
Unclassified epilepsies	0.53	0.18
Febrile seizures	0.58	0.14



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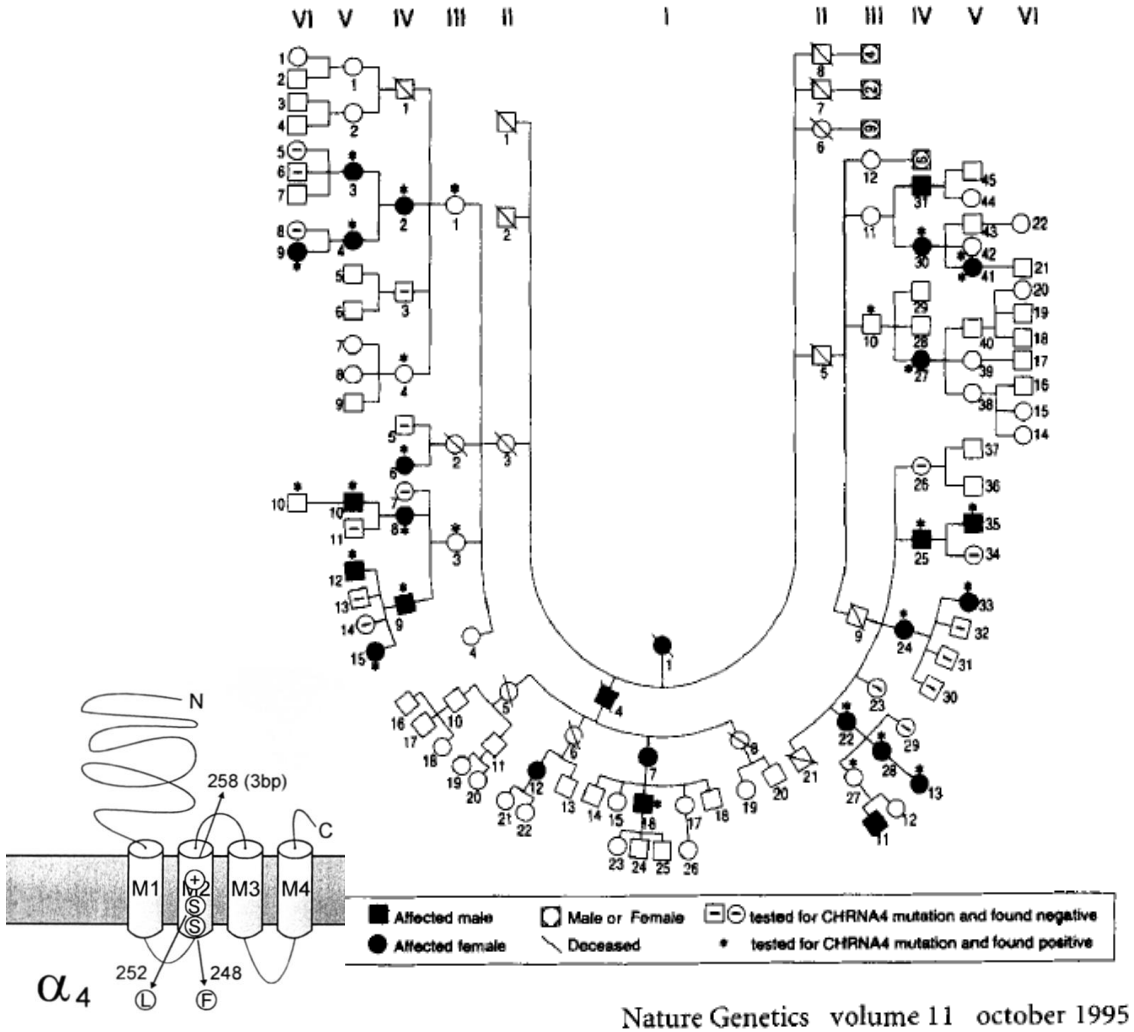
The '*Revolution*': molecular genetics

CHRNA4: the first epilepsy gene (1995)

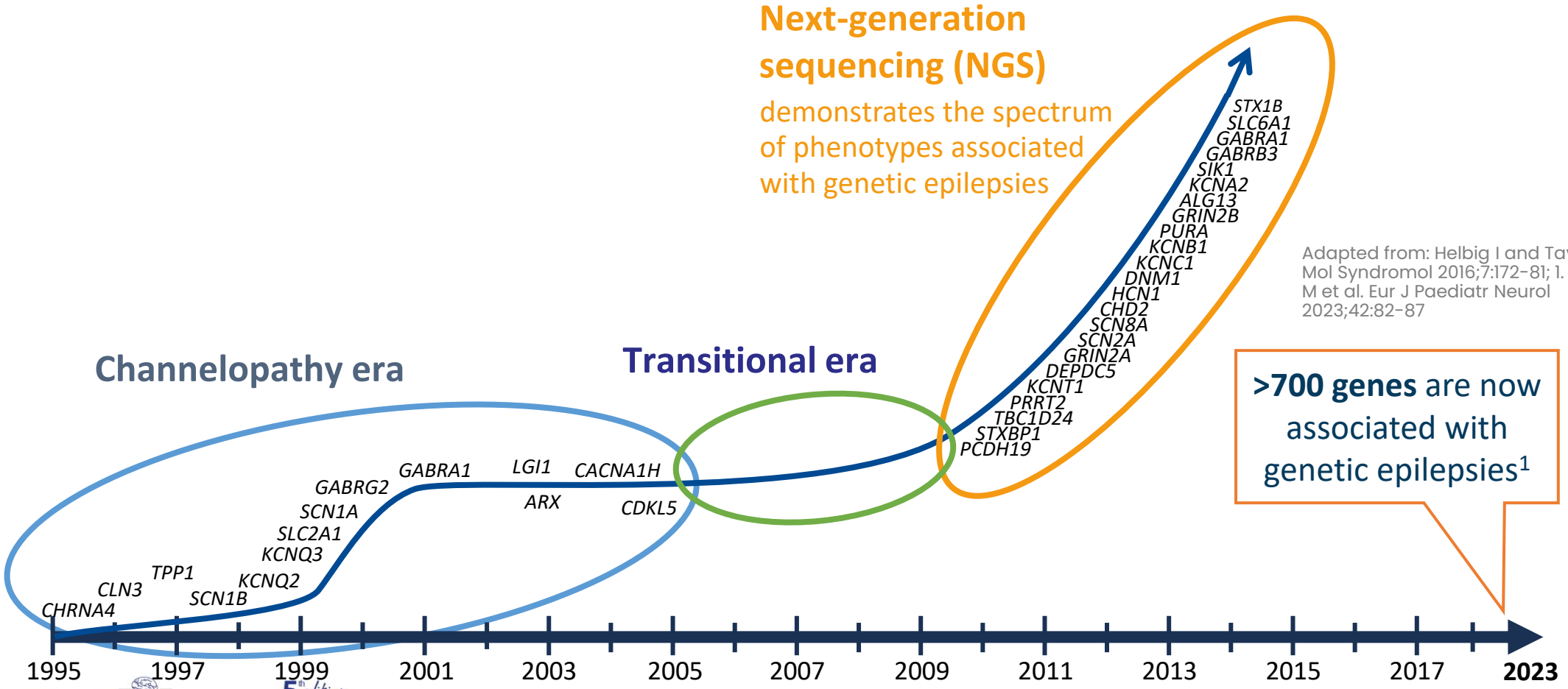
A missense mutation in the neuronal nicotinic acetylcholine receptor α4 subunit is associated with autosomal dominant nocturnal frontal lobe epilepsy

Ortrud K. Steinlein[1], John C. Mulley[2], Peter Propping[1], Robyn H. Wallace[2,3], Hilary A. Phillips[2], Grant R. Sutherland[2,3], Ingrid E. Scheffer[4] & Samuel F. Berkovic[4]



Nature Genetics volume 11 october 1995

The advent of NGS technology has led to an exponential increase in the discovery of novel genetic etiologies



Adapted from: Helbig I and Tayoun AA. Mol Syndromol 2016;7:172-81; 1. Macnee M et al. Eur J Paediatr Neurol 2023;42:82-87

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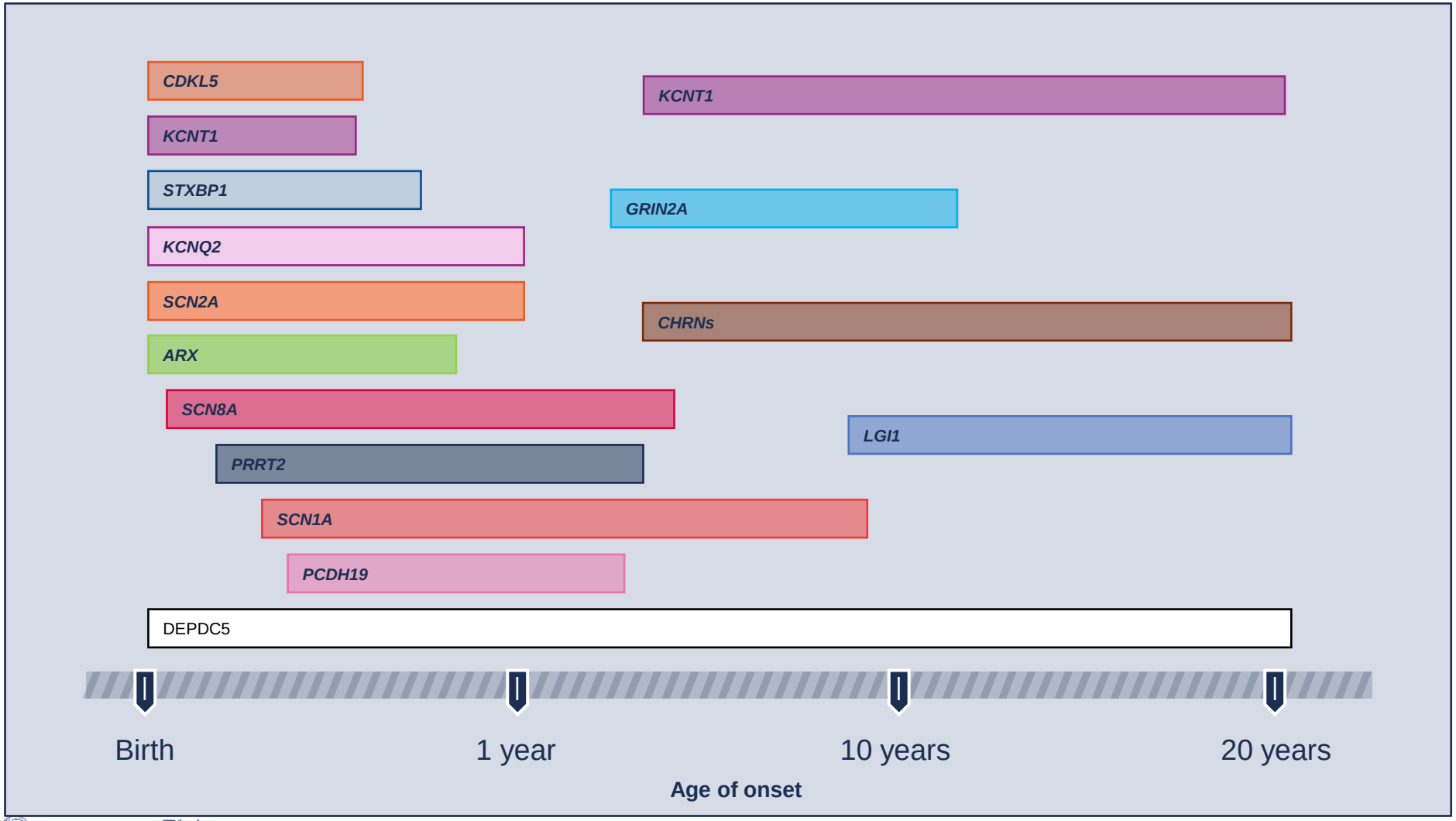
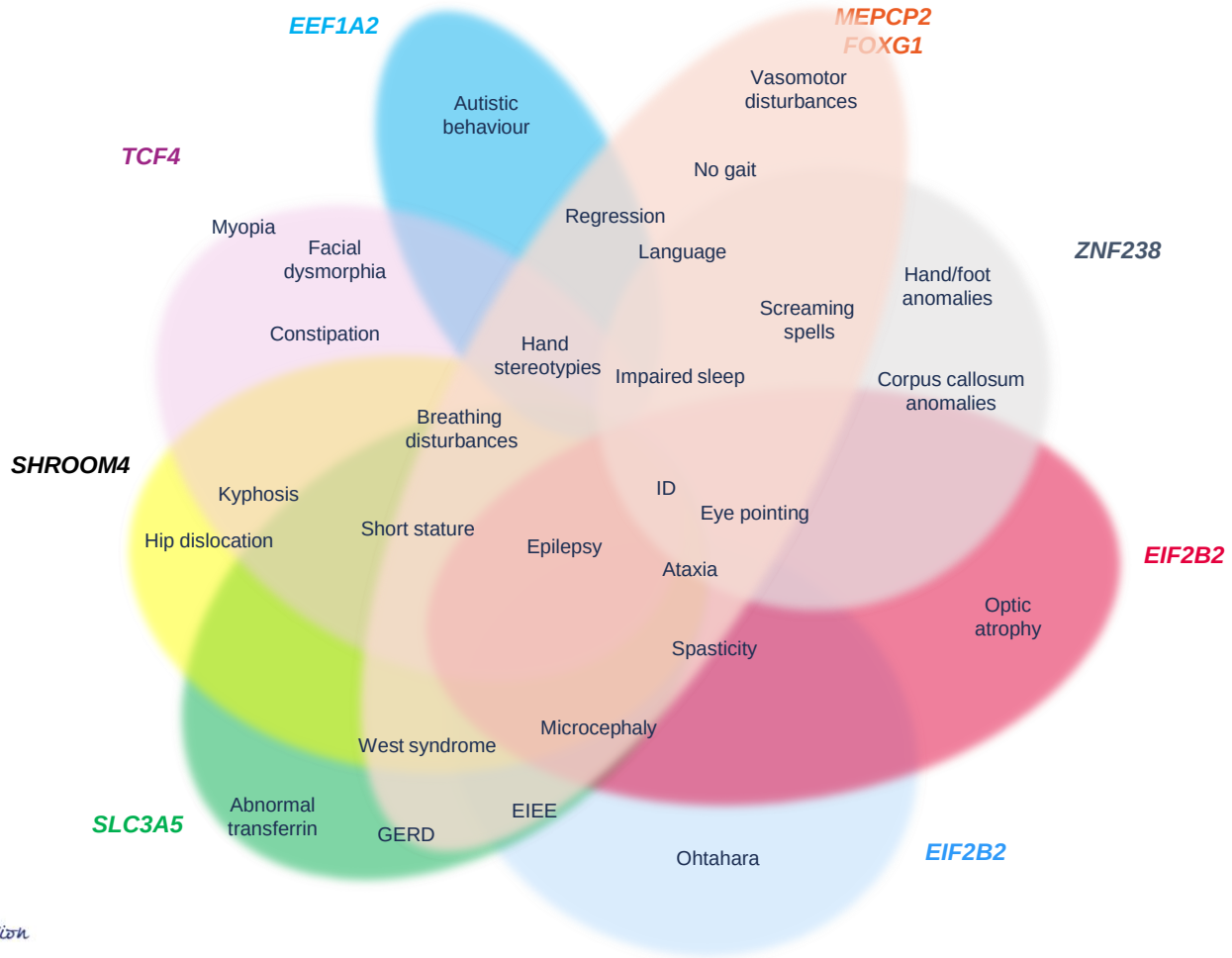
Epilepsy genes by age at presentation



Speaker's own image.

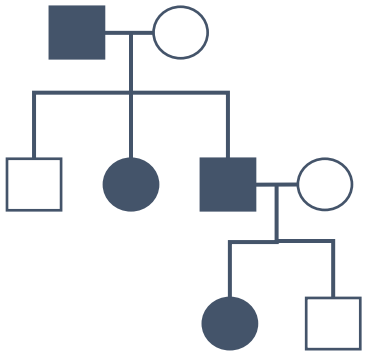
Genetic associations with presentation in DEEs

- DEEs have a spectrum of symptoms and severity, which can make them hard to recognise clinically



DEEs, developmental epileptic encephalopathies; GERD, gastroesophageal reflux disease; EIEE, early infantile epileptic encephalopathy; ID, intellectual disability.
Speaker's own image.

Clinical evaluation

Family history	Clinical history	Neurological examination	Physical examination
			
3-generation pedigree	• Pregnancy and birth • Development • Features of epilepsy • Comorbidities	• Brain MRI • Sleep video-EEG	• Movement disorders • Dysmorphism • Auxological parameters (CC, weight, length) • Muscle biopsy • Fundus oculi • SSEP

EEG, electroencephalogram; MRI, magnetic resonance imaging; SSEP, somatosensory evoked potentials test.
Presenter's own clinical experience.

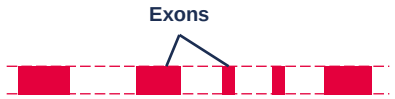
Epilepsies most suitable for genetic testing

(Presumed) monogenic epilepsy + Early onset + Comorbidity + Potential clinical impact

- Developmental and/or epileptic encephalopathies
- Neurodevelopmental disability with epilepsy
- Multi-system disorders including epilepsy
- Progressive myoclonic epilepsies
- Malformations of cortical development and epilepsy

Presenter's own clinical experience.

Which test is appropriate for a patient with suspected genetic epilepsy?

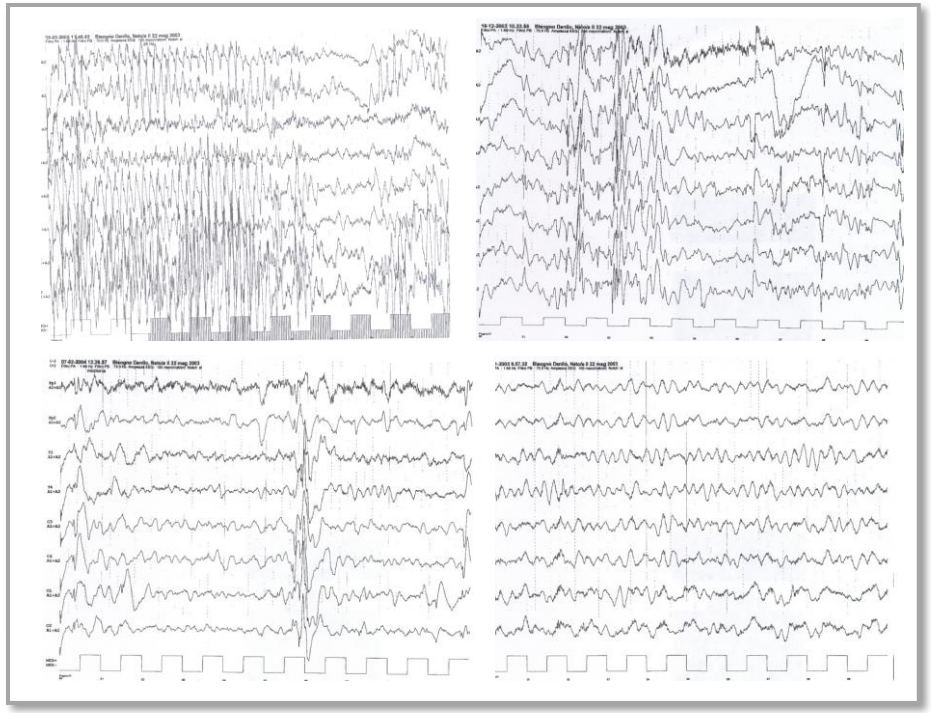
Method	Line and yield	First-line test if…
Single gene sequencing/MLPA 		Dravet syndrome
NGS multigene panel sequencing 	First line (yield 10–40%)	Most DEEs
WES (exons only) 	First line (yield 25–50%)	
WGS (whole genome) 	First line (yield 30–60%)	

NGS, next-generation sequencing; WES, whole exome sequencing; WGS, whole genome sequencing.

Symonds J, McTague A. *Eur J Paediatr Neurol*. 2020;24:15–23 and Presenter's own clinical experience.

Dravet syndrome

- Febrile and afebrile, focal clonic (hemiclonic), generalised clonic or tonic-clonic seizures that occur in the first year of life, later associated with myoclonus, atypical absences, and focal seizures[1,2]
- **Seizures are resistant to most antiseizure medications[1]**
- Developmental delay becomes evident within 12–60 months followed by cognitive impairment and behavioural disorders[1]
- **Prevalence: 1:15,700–40,000 live births[2]**



De Novo Mutations in the Sodium-Channel Gene *SCN1A* Cause Severe Myoclonic Epilepsy of Infancy[3]

Lieve Claes,[1] Jurgen Del-Favero,[1] Berten Ceulemans,[2,3] Lieven Lagae,[3,4] Christine Van Broeckhoven,[1] and Peter De Jonghe[1,2]

[1]Department of Molecular Genetics, Flanders Interuniversity Institute for Biotechnology (VIB), University of Antwerp, and [2]Department of Neurology, University Hospital Antwerp, Antwerp; [3]Epilepsy Center for Children and Youth, Pulderbos, Belgium; and [4]Department of Child Neurology, University Hospital Gasthuisberg, Leuven, Belgium

SCN1A, sodium voltage-gated channel alpha subunit 1.

1. Zuberi SM, et al. Epilepsia. 2022;63(6):1349–97; 2. Cleveland Clinic. Dravet Syndrome. Available at https://my.clevelandclinic.org/health/diseases/22517-dravet-syndrome. Accessed June 2024; 3. Claes L, et al. Am J Hum Genet. 2001;68(6):1327–32.

SCN2AITALIA
FAMIGLIE IN RETE

SCN2A-related disorders: a spectrum of neurodevelopmental disorders encompassing developmental and epileptic encephalopathy (DEE) and intellectual disability (ID) or autism spectrum disorder (ASD) without epilepsy

doi:10.1093/brain/awx054 BRAIN 2017: 140; 1316–1336 | 1316
BRAIN
A JOURNAL OF NEUROLOGY

Genetic and phenotypic heterogeneity suggest therapeutic implications in *SCN2A*-related disorders

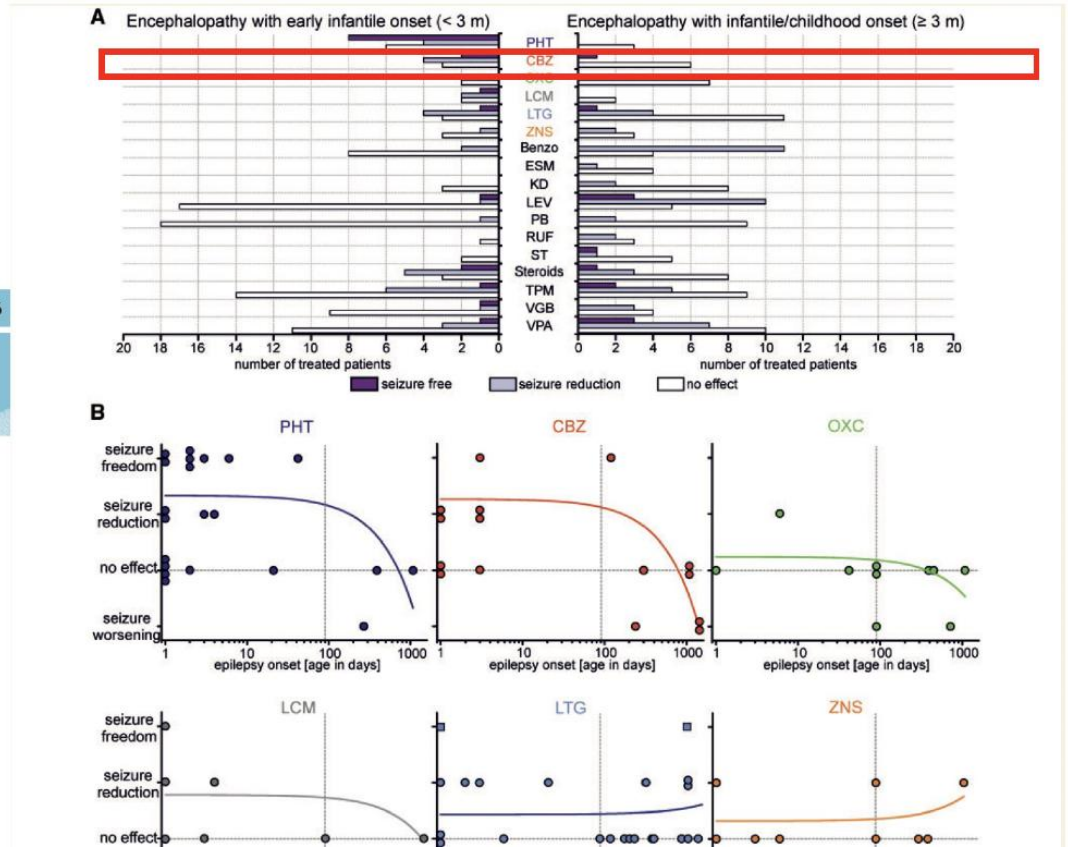


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Figure 2 Neurodevelopmental Features in Individuals With *STXBP1*-DEE Stratified per Age Range at Seizure Onset

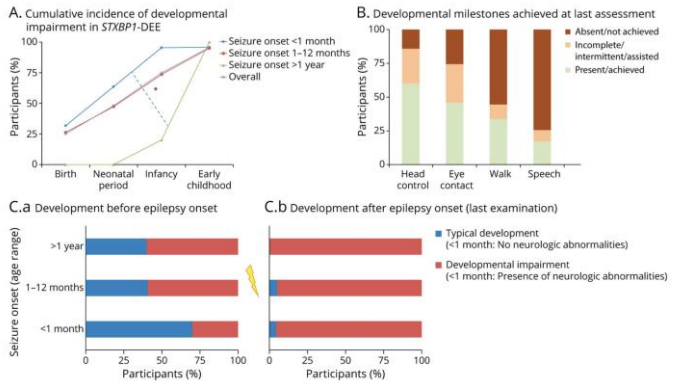
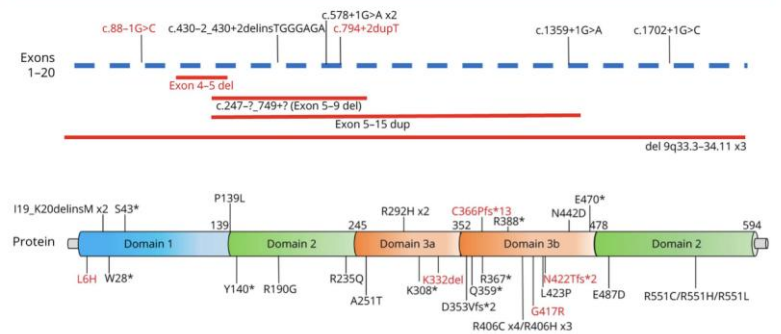


Figure 1 *STXBP1* Variants Over Exons and Linear Protein Structure

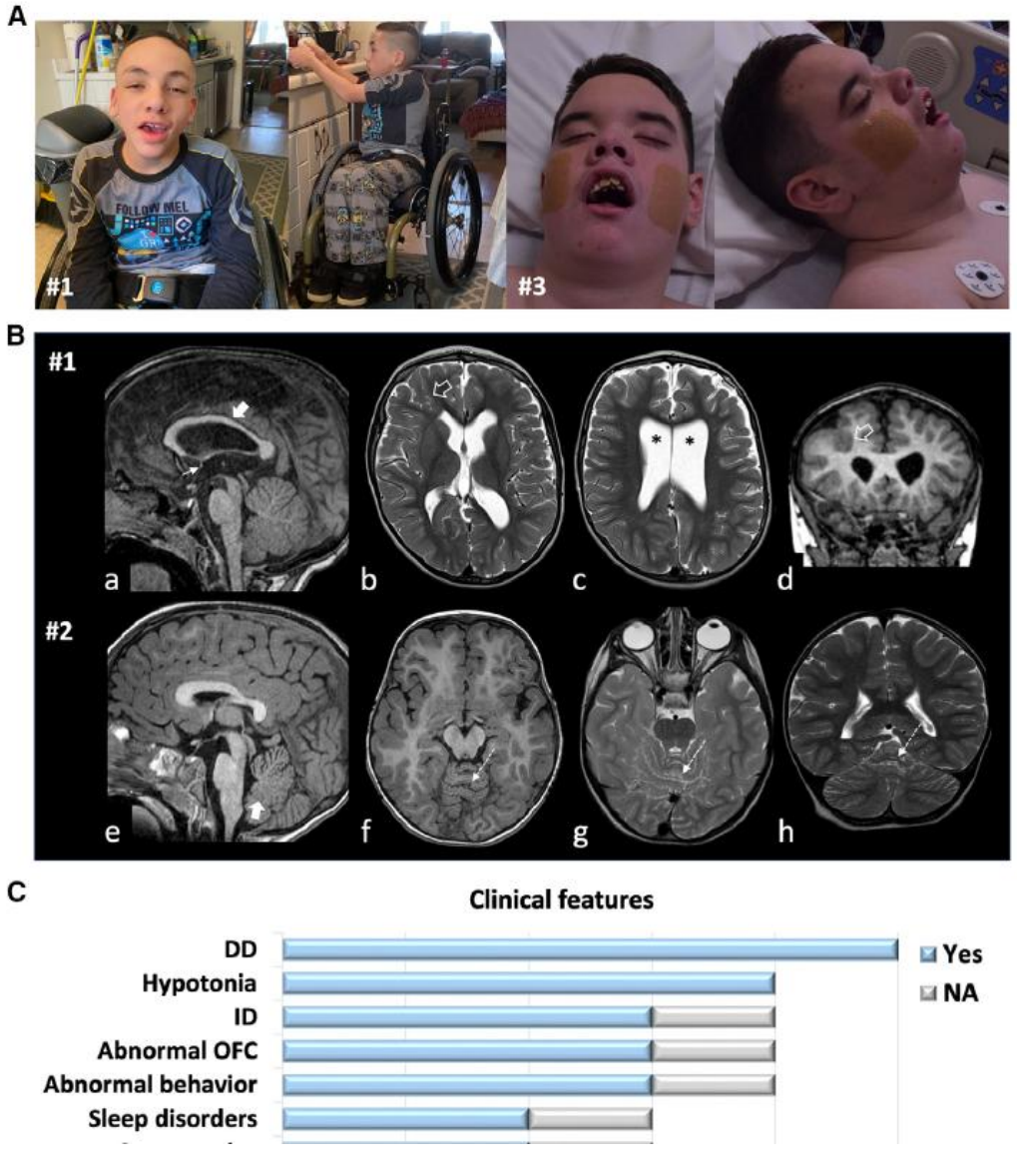


Novel variants are highlighted in red.

STXBP1

New Genes?

Marcello Scala, MD, PhD

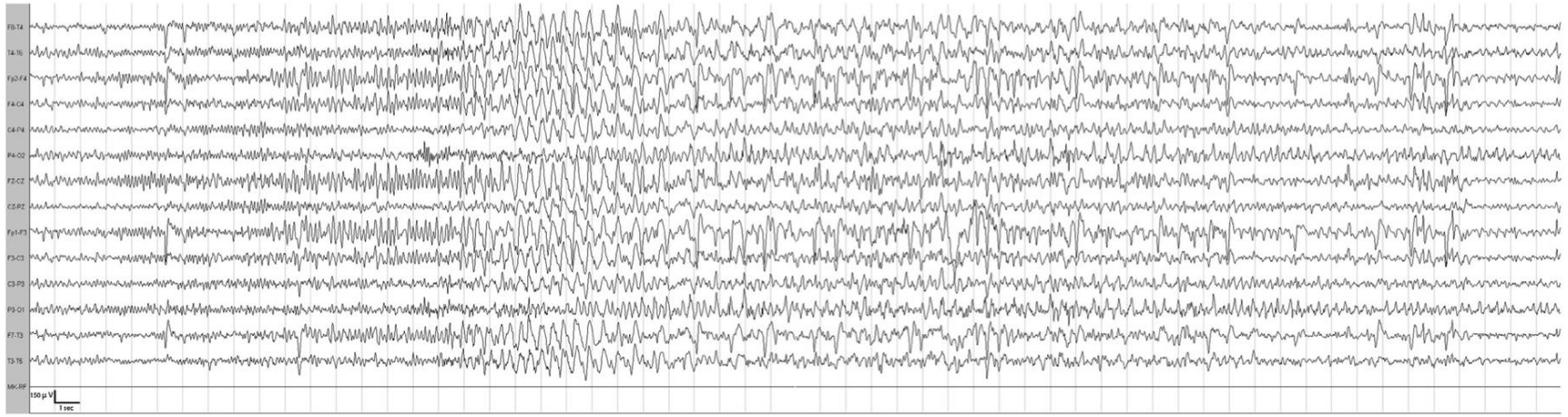


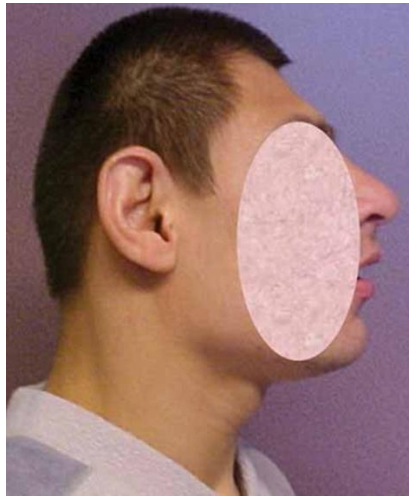
Marcello Scala, Valeria Tomati, Matteo Ferla, ..., Vincenzo Salpietro, Nicoletta Pedemonte, Federico Zara

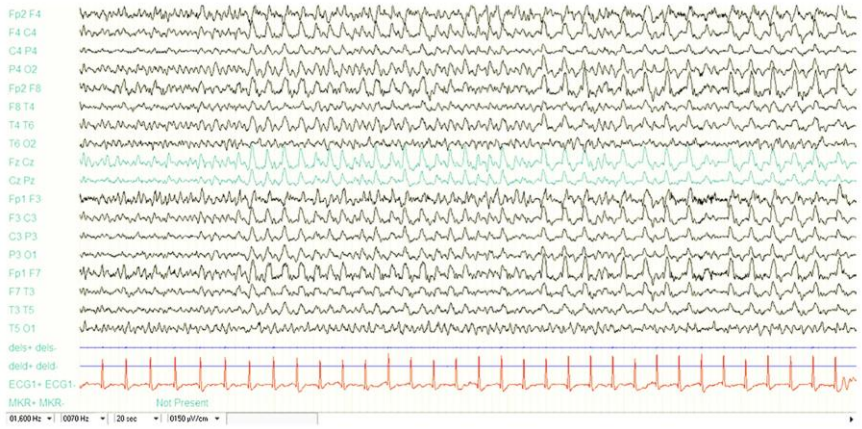
Correspondence

v.salpietro@ucl.ac.uk (V.S.), nicolettapedemonte@gaslini.org (N.P.)

In this study, we identify *de novo* missense variants in *DENND5B* as the cause of a neurodevelopmental disorder with dysmorphism and epilepsy. We show that these variants impair intracellular vesicle trafficking, lipid uptake and intracellular distribution, and protein folding, leading to complex neurological manifestations.

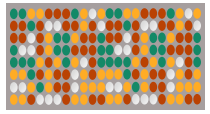
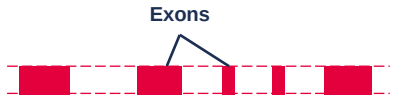




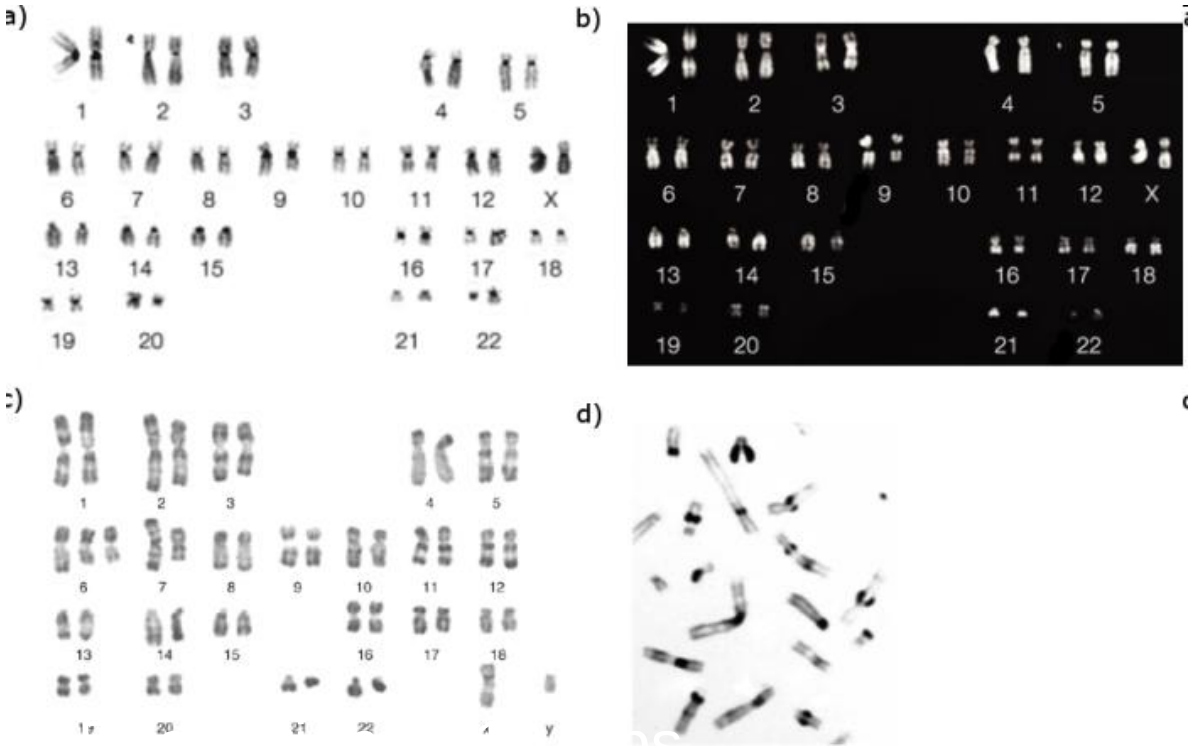


- Dysmorphic features may be mild
- The degree of ID from mild to severe
- Invariably, seizures occur in infancy and are intractable. A variety of types has been described
- Brain atrophy with ventricle dilatation.
- In most individuals the breakpoints in 14q were detected in the terminal band 14q32.

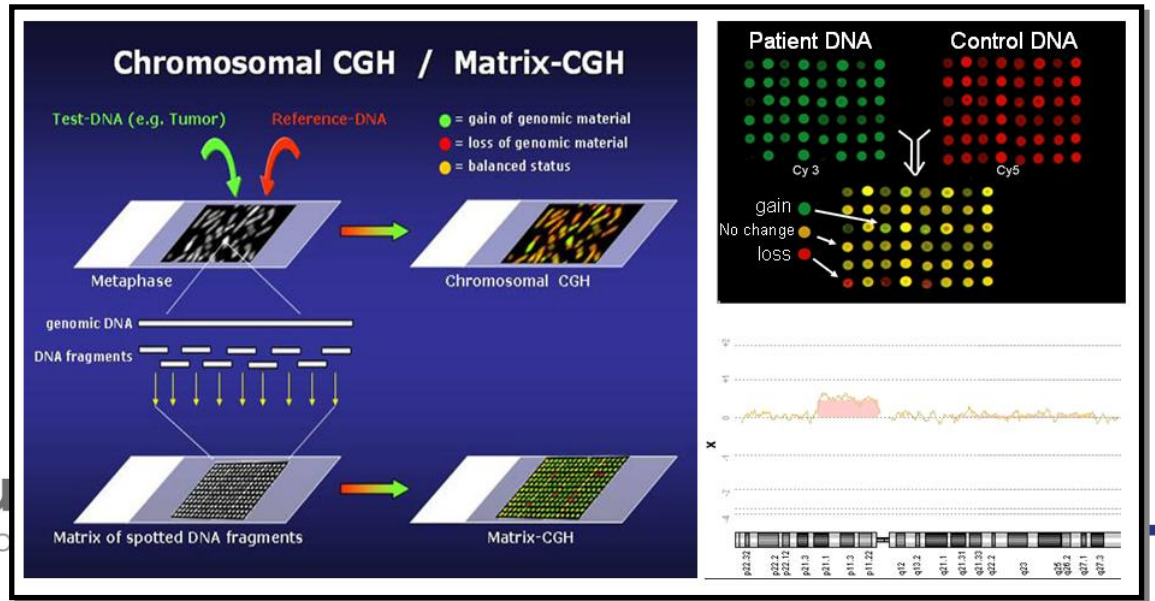
Which test is appropriate for a patient with suspected genetic epilepsy?

Method	Line and yield	First-line test if…
Karyotyping 		Specific syndrome suspected: Ring chr. 20 (trisomy)
Chromosomal microarray 	Second line (yield ~10%)	Multi-gene system pathology indicating multi-gene involvement
Single gene sequencing/MLPA 		Dravet syndrome
NGS multigene panel sequencing 	First line (yield 10–40%)	Most DEEs
WES (exons only) 	First line (yield 25–50%)	
WGS (whole genome) 	First line (yield 30–60%)	

NGS, next-generation sequencing; WES, whole exome sequencing; WGS, whole genome sequencing. Symonds J, McTague A. *Eur J Paediatr Neurol*. 2020;24:15–23 and Presenter's own clinical experience.



Large aberrations (10 Mb)
Balanced translocations
Ring chromosomes



Chromosomal del/dup
Unbalanced translocations

- Chromosomal Abnormalities
  - Numeric
    - Polyploidy
      - Tryploidy
      - Tetraploidy
    - Aneuploidy
      - Trisomy
      - Monosomy
      - Extranumerary Markers
  - Structural
    - Translocations
      - Reciprocal
      - Robertsonian
    - Insertions
    - Duplications
    - Inversions
    - Deletions
      - Terminal
      - Interstitial
    - Ring Chromosomes
    - Isochromosomes

ELSEVIER

Brain & Development 27 (2005) 370–377

of Child Neurology

www.elsevier.com/locate/braindev

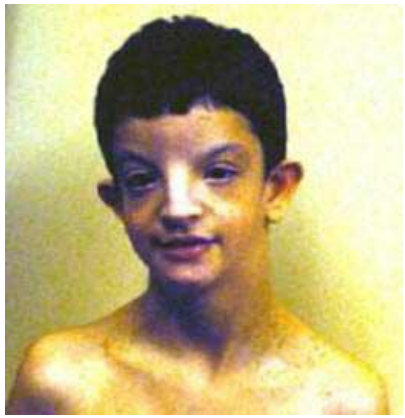
Original article

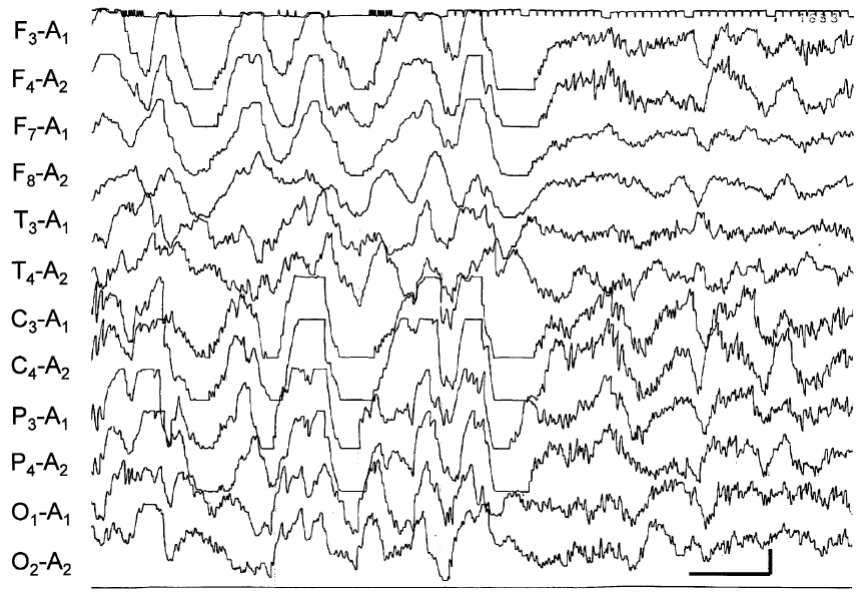
An analysis of epilepsy with chromosomal abnormalities☆

Hideo Yamanouchi[a,*], George Imataka[a], Eiji Nakagawa[a], Akihisa Nitta[a], Naomitsu Suzuki[a], Jun-ichi Hirano[a], Hiroshi Suzumura[a], Hiroshi Watanabe[b], Osamu Arisaka[a], Mitsuoki Eguchi[a]

Patients with chromosomal abnormality found in NICU

Chromosomal abnormality	Number of patients	Number of patients with epilepsy
Trisomy 21	71	5
Trisomy 18	29	1
Trisomy 13	8	1
Trisomy 22	1	0
Trisomy 10, mosaic	1	0
Trisomy 8, mosaic	1	0
del (22)(q11.2)	3	0
del(4)(p16.3)	2	na
del(13)(q21.2q31.2) t(2;4)(q24.2;p14)	1	1
del(9)(q22.3q32)	1	0
del(8)(q13.1q21.2)	1	0
21q−	1	1
r (12)(p13;q24)	1	0
46, XY, -6, +der(6)t(6;11) (q25.1;q23.3)	1	1
46, XY/46, XY, t(2:13)(q31;q21.2)	1	0
ins(14;16)(p12;p13.3)	1	0
47 XX, +der 15 t(3:15)(q23:q11.2) mat	2	0
Add(7)(p22)	1	0
Add (6)(q25.3)	1	0
Total	128	10





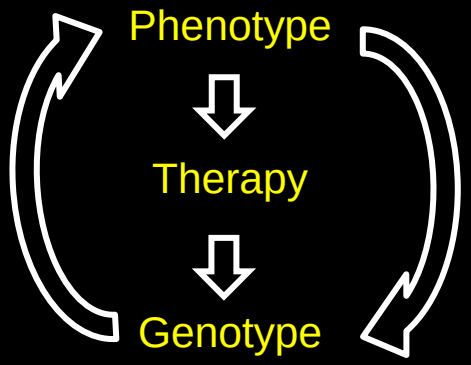
?

La **Sindrome di Angelman** è causata dall'assenza di una porzione del cromosoma 15 (porzione contrassegnata come 15q11-q13). La malattia si osserva solo nelle persone in cui la mancanza riguarda il cromosoma 15 di origine materna.

I pazienti con Sindrome di Angelman possono essere suddivisi in 5 specifiche classi eziologiche:
1) delezione della regione SA/SPW sulla copia del cromosoma 15 (regione 15q11-q13) ereditato dalla madre;
2) disomia uniparentale paterna;
3) difetto del centro dell'imprinting (IC);
4) mutazione del gene UBE3A;
5) meccanismi genetici non ancora identificati.

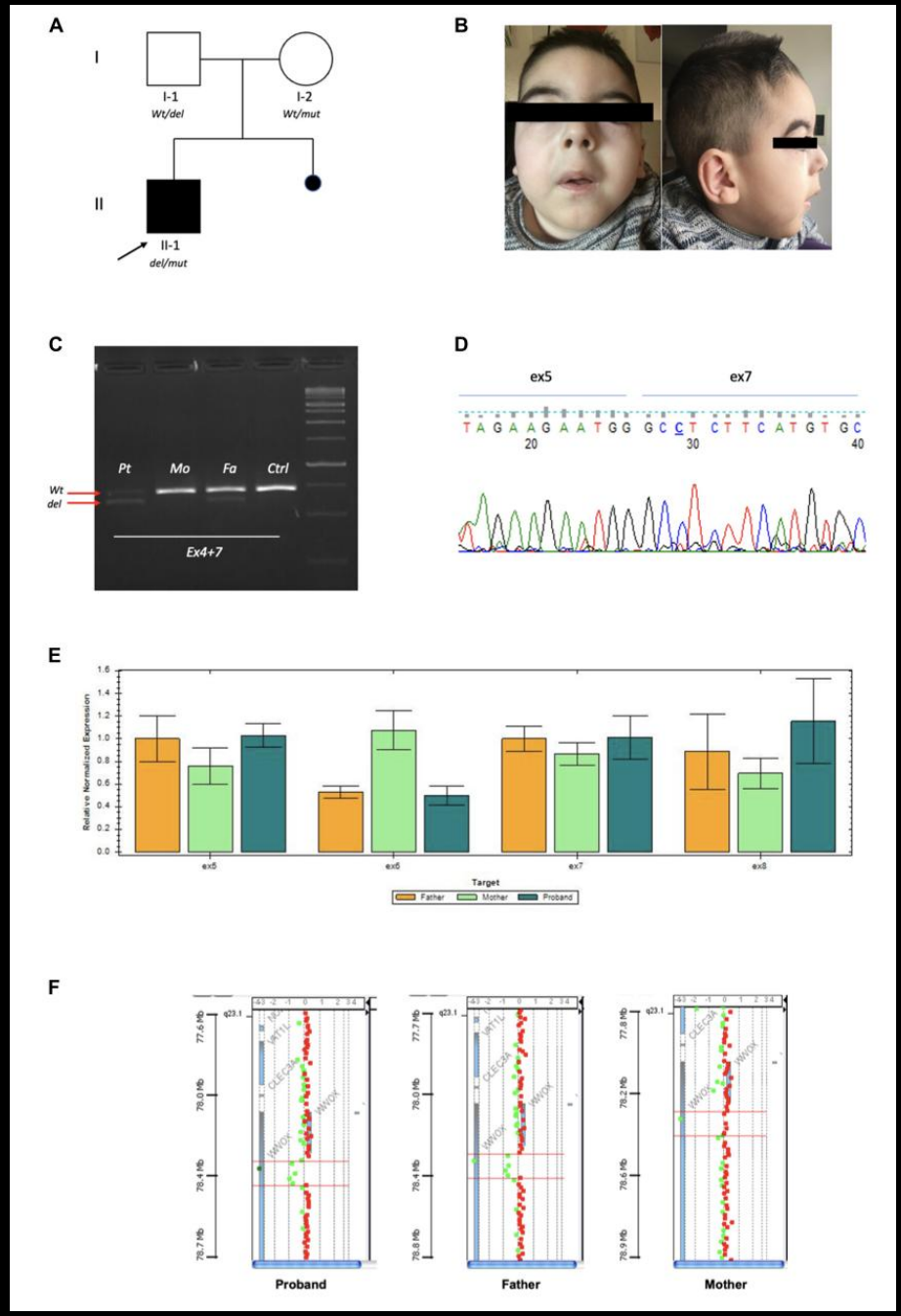
Gli individui con delezioni del cromosoma 15q11-q13 hanno un quadro clinico più severo e sono più inclini a sviluppare una grave epilessia.

INTERNATIONAL ANGELMAN DAY FEB 15



A Phenotypic-Driven Approach for the Diagnosis of WOREE Syndrome

Antonella Riva[1,2†], Giulia Nobile[2†], Thea Giacomini[2,3], Marzia Ognibene[1], Marcello Scala[2,4], Ganna Balagura[5], Francesca Madia[1], Andrea Accogli[6,7], Ferruccio Romano[2], Domenico Tortora[8], Mariasavina Severino[8], Paolo Scudieri[1,2], Simona Baldassari[1], Ilaria Musante[1], Paolo Uva[9], Vincenzo Salpietro[2,4], Annalaura Torella[10,11], Vincenzo Nigro[10,11], Valeria Capra[1], Lino Nobili[2,3], Pasquale Striano[2,4], Maria Margherita Mancardi[2,3], Federico Zara[1,2‡] and Michele Iacomino[1,9‡]*



Genetic testing tools

*only WGS, ** Turnaround times vary by lab; times stated taken from a survey of labs obtained from concertgenetics.com; ASD: autism spectrum disorder;
DD: developmental delay; ID: intellectual disability; VUS: variant of uncertain significance
Taylor A et al. Genes (Basel) 2021;12:818; 1. Sheidley BR et al. Epilepsia 2022;63:375-87; 2. Mei D et al. Mol Diagn Ther 2017;21:357-73

	Chromosomal microarray	Single gene sequencing	Targeted gene panels	Whole exome/genome sequencing (WES/WGS)
Variants identified	• Large chromosomal deletions/ duplications • High resolution (up to 25 kb)	Sequence variants, small deletions (<50 bp), or insertions	• Sequence variants, small deletions, or insertions • Copy number variations (CNVs)	• Sequence variants, small deletions, or insertions • CNVs • Structural rearrangements*
When to use	Multiple congenital anomalies, ID or DD, and ASD	For segregation analysis and family testing	• Clearly defined phenotype • Short differential diagnosis list	• Unclear/large differential diagnosis • Non-specific clinical findings • Specific test unavailable
Limitations	• Cannot identify balanced rearrangements • Cannot identify sequence variants or small copy number variants ≤1–10 kb	Very few conditions are monogenic	• Not suitable if no primary phenotype • Not suitable if differential diagnosis is long	• Very expensive • Long turnaround time • High chance of VUS • Secondary findings • Incidental findings • Limited understanding of non-coding variants*
Diagnostic yield	9%[1]	Very low[1]	Variable between condition/ phenotype (up to ~50%[2])	8-86%
Turnaround time**	2–6 weeks+	1–4 weeks+	2–6 weeks+	4–16 weeks+

DS
67 articles

LGS
17 articles

DS and LGS
7 articles

Incidence and prevalence

Estimated affected individuals per 100 000 people

- Wide range in estimates for LGS may reflect heterogeneity in diagnosis

Genotype

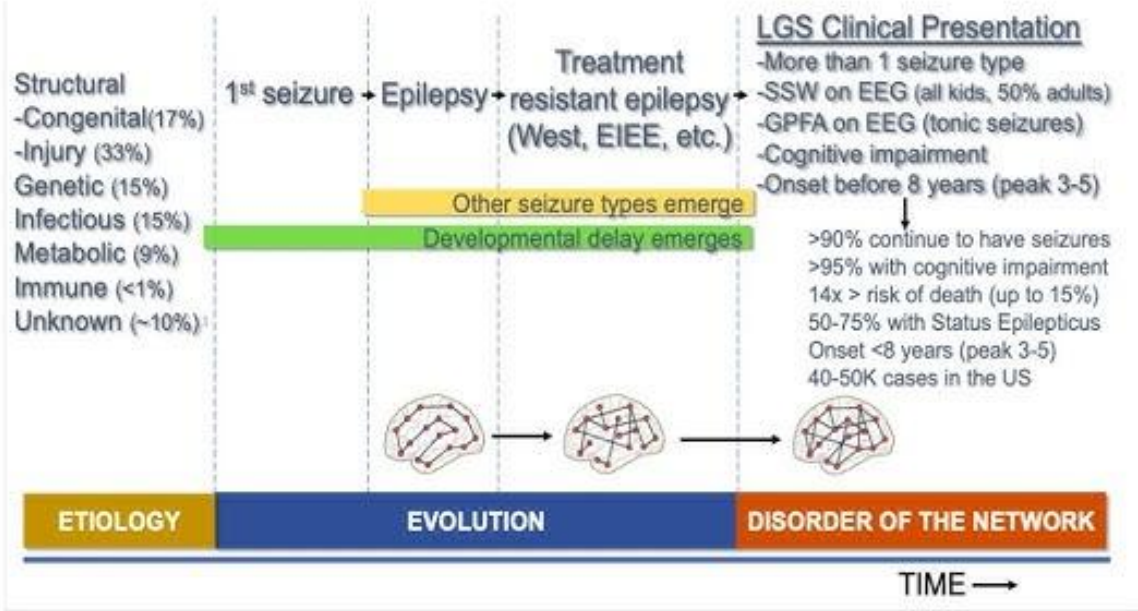
SCN1A

- *SCN1A* screening included in all genetic studies
- *SCN1A* variant reported in ≥70% of people with DS
- Paucity of data on LGS genotyping

Diagnosis

- Age at diagnosis
  - DS: **1.6–9.2 years**
  - LGS: **2–15 years**
- Diagnostic delay and misdiagnosis were reported for both conditions, but especially for LGS

Evolution of LGS Over Time



nature genetics

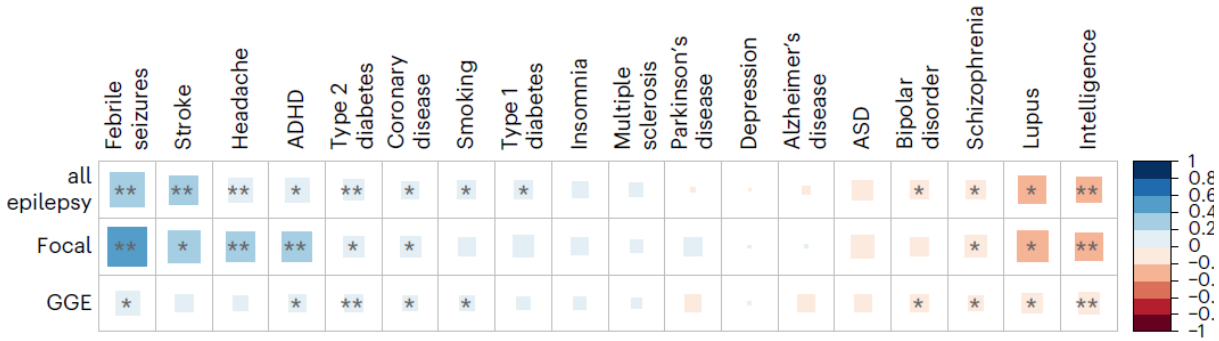
Article

https://doi.org/10.1038/s41588-023-01485-w

GWAS meta-analysis of over 29,000 people with epilepsy identifies 26 risk loci and subtype-specific genetic architecture

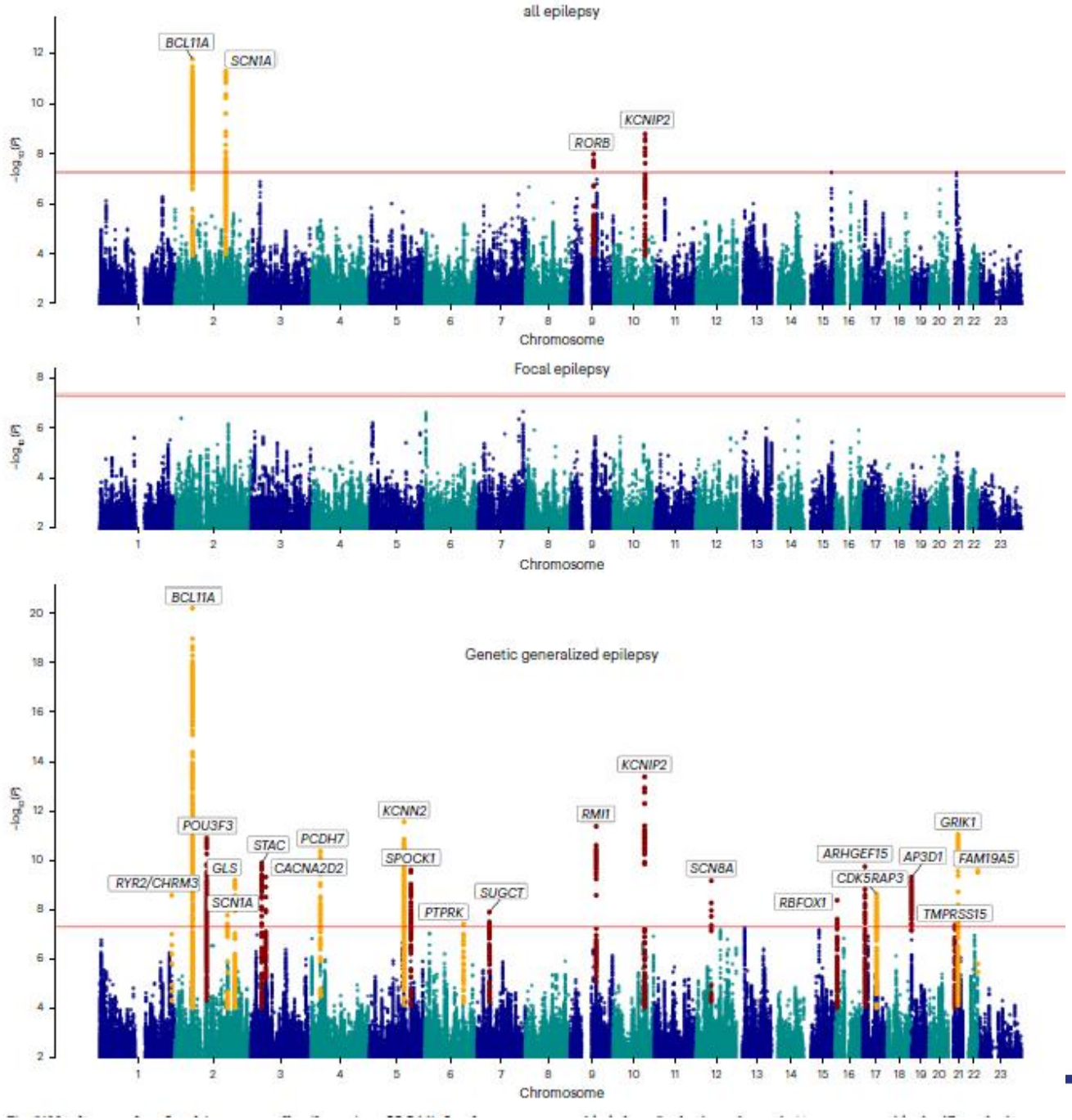
Received: 7 June 2022

International League Against Epilepsy Consortium on Complex Epilepsies*

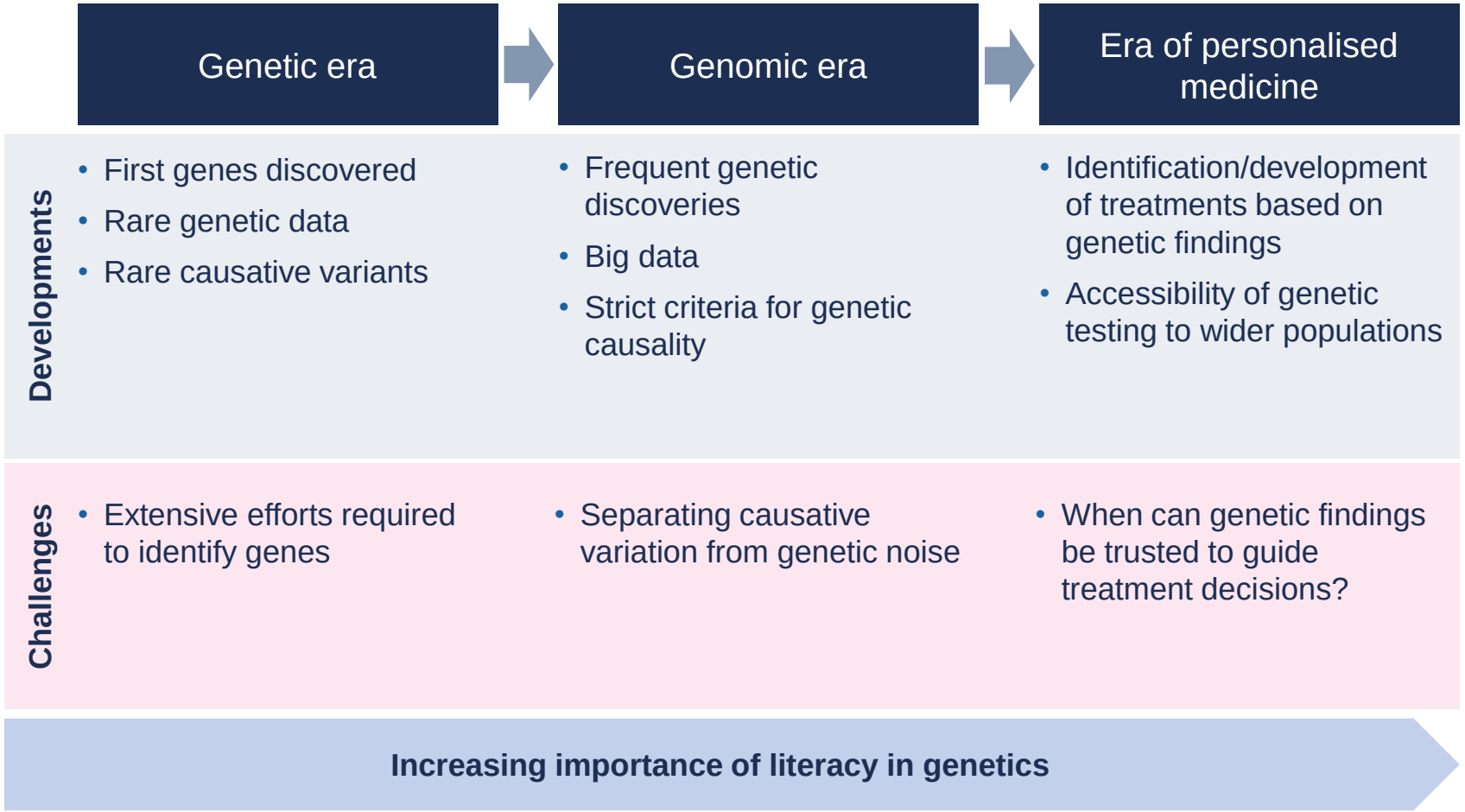


Genetic correlations of epilepsy with other phenotypes denoted by color scale from −1 (red; negatively (anti-)correlated) to +1 (blue; positively correlated).

Significant correlations ($P < 0.05/54 = 0.0009$) were found with febrile seizures, stroke, hea



The three stages of epilepsy genetics



Presenter's own clinical experience.

Examples of potential therapeutic approaches

GABA: gamma-aminobutyric acid; GoF: gain of function; LoF: loss of function; mTOR: mammalian target of rapamycin
1. Bayat A et al. Neurotherapeutics 2022;19:1353-67; 2. Keam SJ. Drugs 2023;83:819-24; 3. Schulz A et al. N Engl J Med 2018;378:1898-907

Gene →  **Clinically available targeted therapy**

DEPDC5	Everolimus and other mTOR inhibitors
GABRB3	LoF: GABAergic enhancers, e.g., phenobarbital, vigabatrin (GoF: avoid GABAergic enhancers)
KCNQ2	Sodium channel blockers (LoF)
MECP2	Trofinetide[2]
SCN1A	LoF: Stiripentol (+ valproate + clobazam), fenfluramine, cannabidiol; Avoid sodium channel blockers
SCN2A	GoF: Sodium channel blockers (LoF: avoid sodium channel blockers)
SLC1A2	Ketogenic diet
SLC6A1	Avoid GABA-potentiating drugs
TPP1 (*CLN2*)	Enzyme replacement therapy (ERT)[3]
TSC1 / TSC2	Everolimus and other mTOR inhibitors

Drug Metabolizing Enzymes

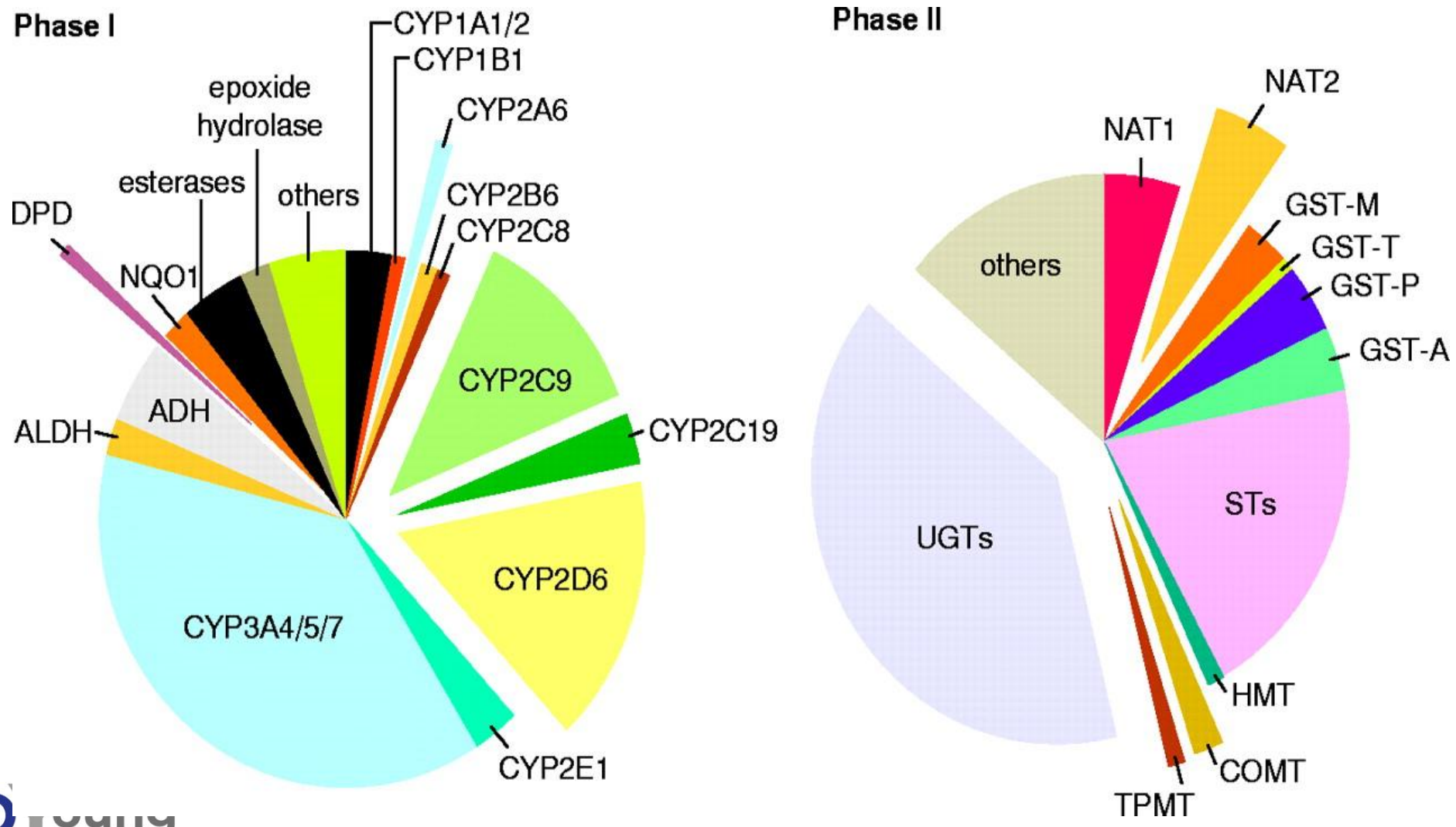
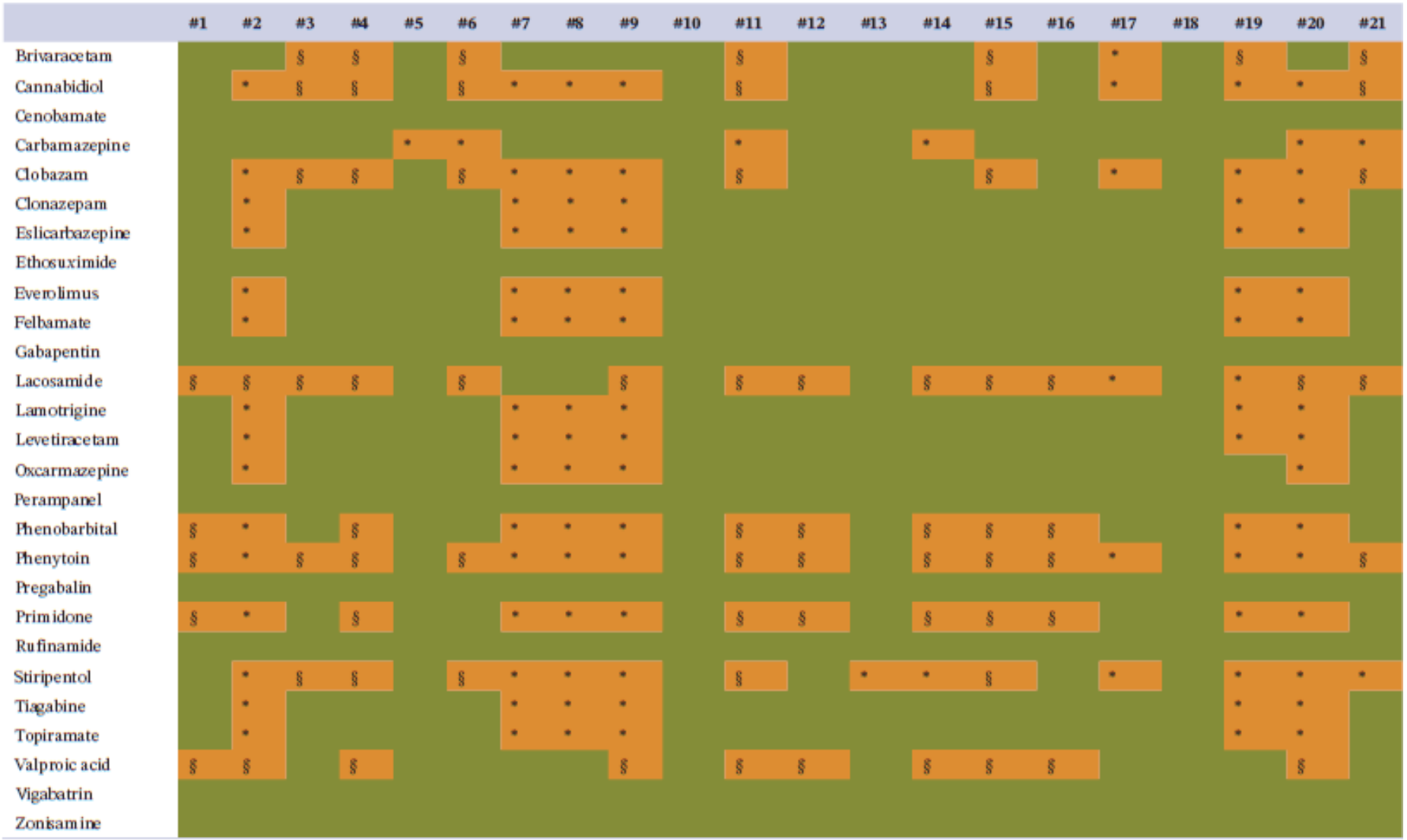


TABLE 2 Personalized drug selection suggestions based on pharmacogenomic data.



Note: Orange = need of monitoring due to: *Reduced chance of optimal response, §Increased risk of adverse events; green = optimal safety and efficacy profile.

TABLE 1 *CYP1A2*, *CYP2C9*, *CYP2C19*, *EPHX1*, and *ABCB1* genotypes, phenotypes, and frequencies.

Gene	Genotype	Phenotype	Frequency
CYP1A2	*1/*1F	EM	15/21 (71.4%)
	*1F/*1F	FM	6/21 (28.6%)
CYP2C9	*1/*1	EM	11/21 (52.4%)
	*1/*2	IM	5/21 (23.8%)
	*1/*3		4/21 (19%)
	*2/*3	PM	1/21 (4.8%)
CYP2C19	*1/*1	EM	10/21 (47.6%)
	*1/*17		3/21 (14.3%)
	*1/*17	FM	1/21 (4.8%)
	*1/*2	IM	6/21 (28.5%)
	*2/*2	PM	1/21 (4.8%)
EPHX1	337T>C (CC)	↓ efficacy CBZ	6/21 (28.5%)
ABCB1	3489 + 80C>T (CC)	Drug-resistant	6/21 (28.5%)
	3489 + 80C>T (CT or TT)	Drug-sensitive	7/21 (33.3%)

Abbreviations: EM, extensive metabolizer (standard); FM, fast metabolizer; IM, intermediate metabolizer; PM, poor metabolizer.

Colour shade indicate to distinguish the different aplotypes and their effect on cytocromes.

Thank you!

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