


Genetic Testing in Epilepsy

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Outline

- Basic genetic principles (for neurologist)
- Genetic testing methods and interpretation of results
- Implication of therapeutic decision-making

Epilepsy Classification

- Focal epilepsies
- Generalized epilepsies
- Developmental and epileptic encephalopathy (DEE)

Genetic Epilepsies

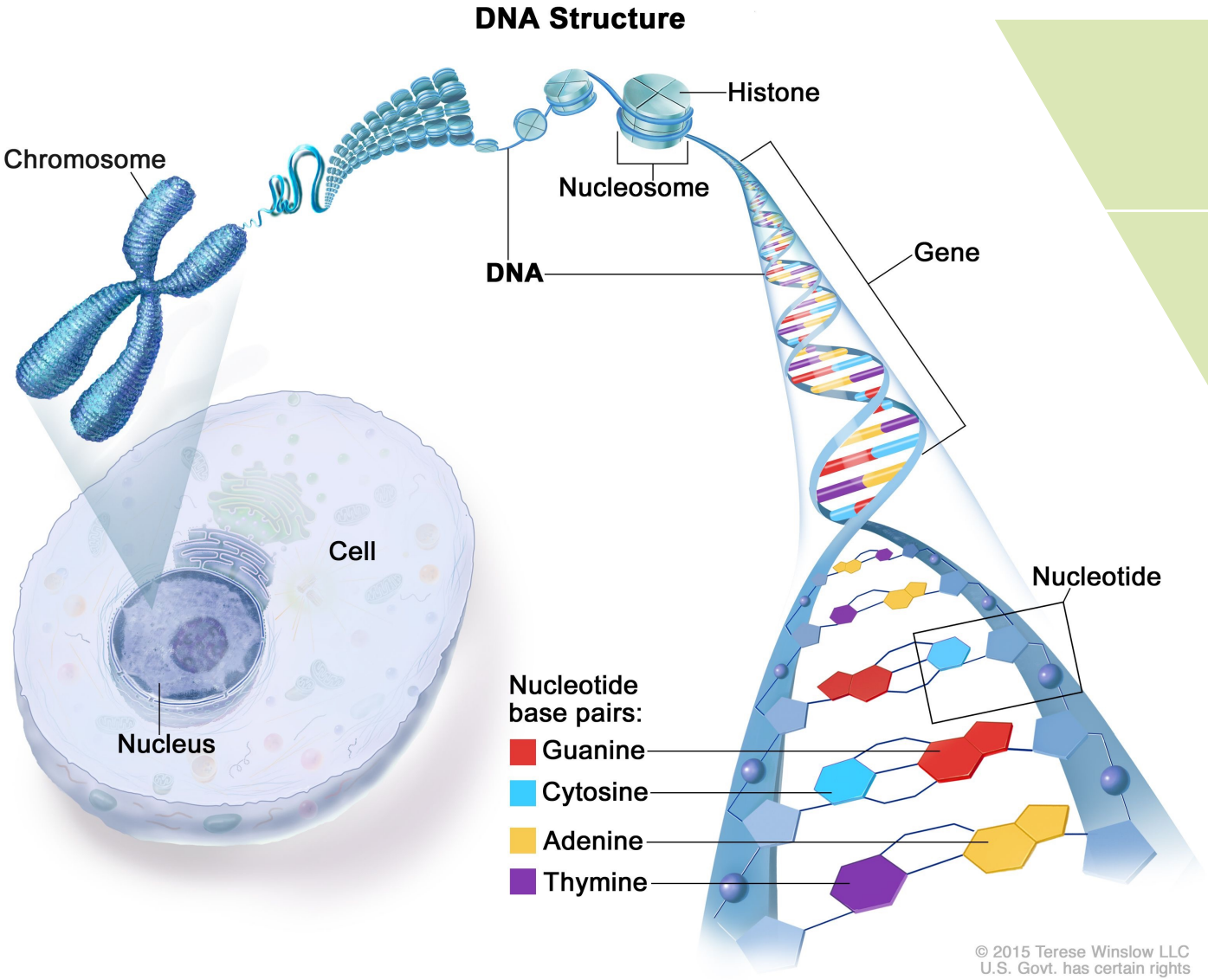
- A known or presumed underlying genetic etiology
- Lack of an acquired cause such as trauma or infection
- Non-inheritable vs Heritable

Krev I, ILAE Genetics Commission, Epileptic Disord 2022

Basic Genetic Principles

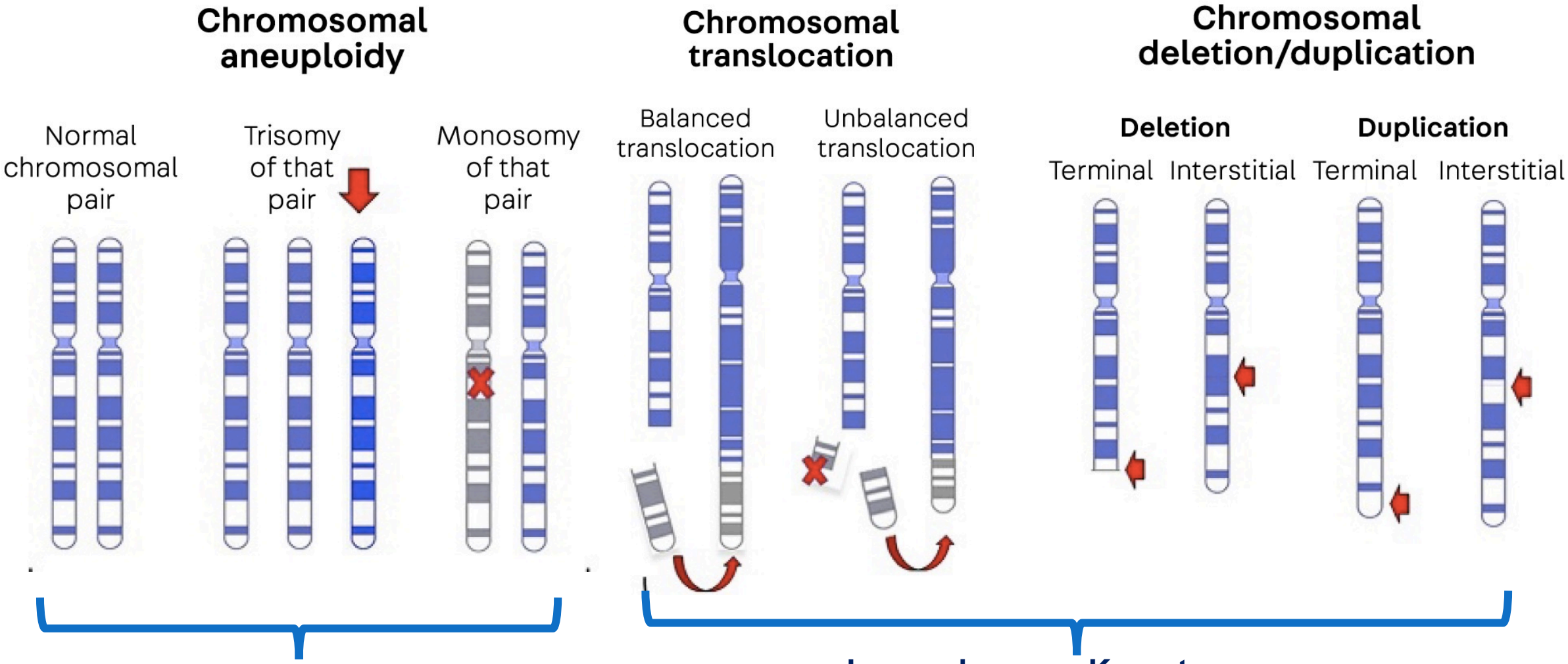
- Monogenic epilepsises (single gene)
  - Basic inheritance patterns (AD, AR, X-linked, mitochondrial)
  - De novo variant occurs most often during gametogenesis
  - Mosaic arises in the post-zygotic stage
  - Causal genetic variation: single nucleotide variants (SNV), copy number variants (CNV: deletion, duplication), repeat expansions, complex structural rearrangements
- Epilepsy with complex genetic patterns
  - Genetic generalized epilepsy & non-acquired focal epilepsy
  - Risk in family 3-8%
  - Multifactorial etiology: polygenic scores

Genetic Testings in Epilepsy



- Chromosomal study
- Chromosomal microarray (CMA)
- Targeted gene sequencing
- Whole exome sequencing (WES)
- Whole genome sequencing (WGS)

Genetic Variability at the Chromosome Level

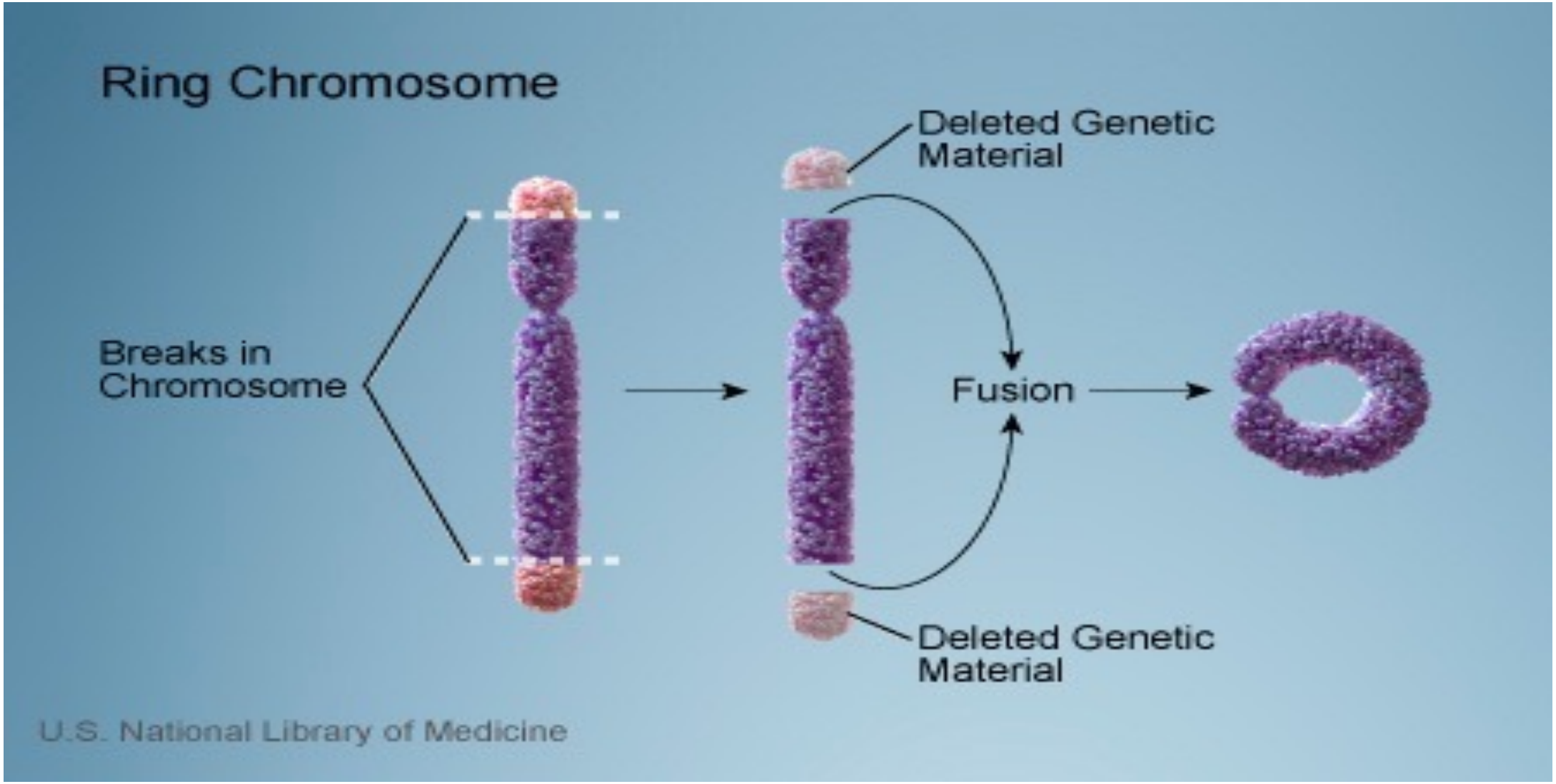


Karyotype and CMA

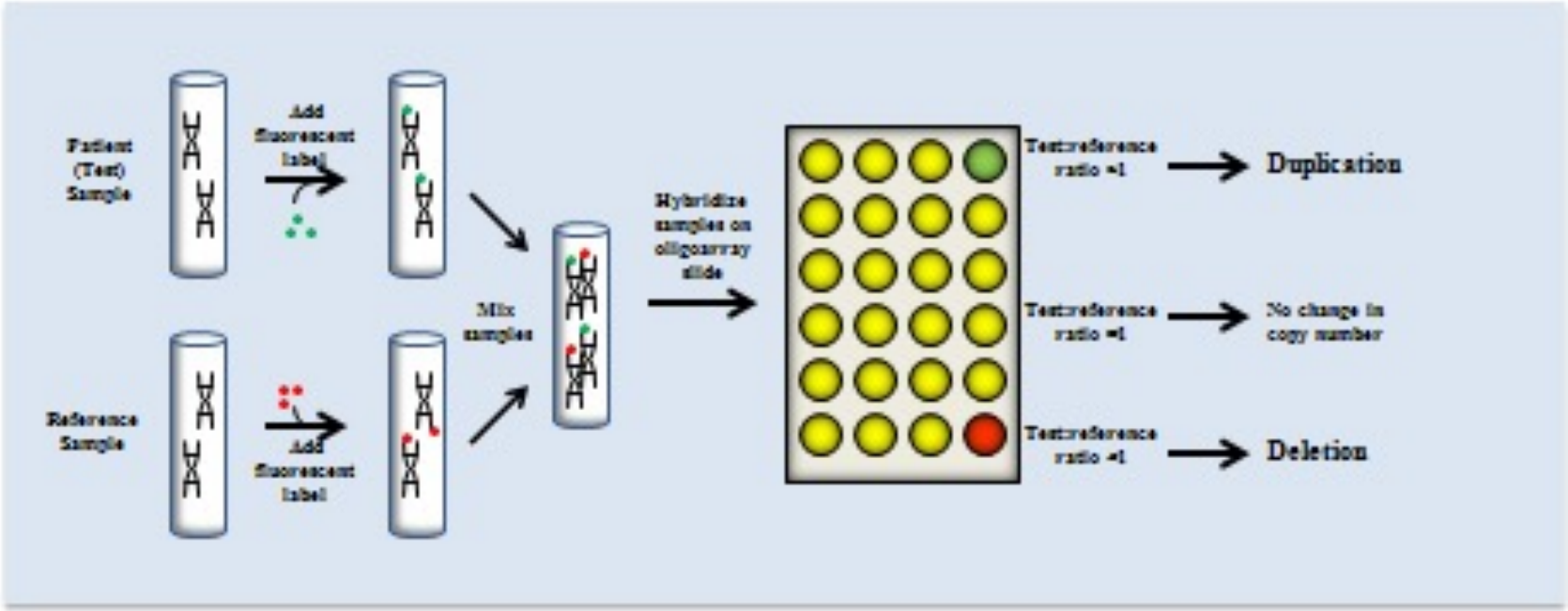
Large changes: Karyotype
Small changes: FISH or CMA
CMA will miss balanced translocation

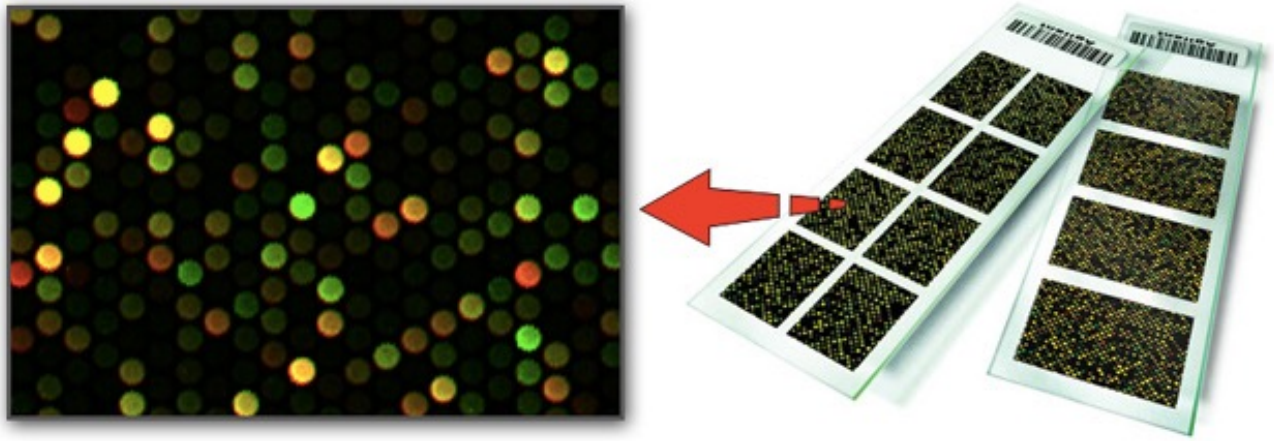
Silveira-Moriyama L, Continuum 2018

Ring Chromosome



Chromosomal Microarray (CMA) reported as copy number variation (CNV)‘gain or ‘loss’

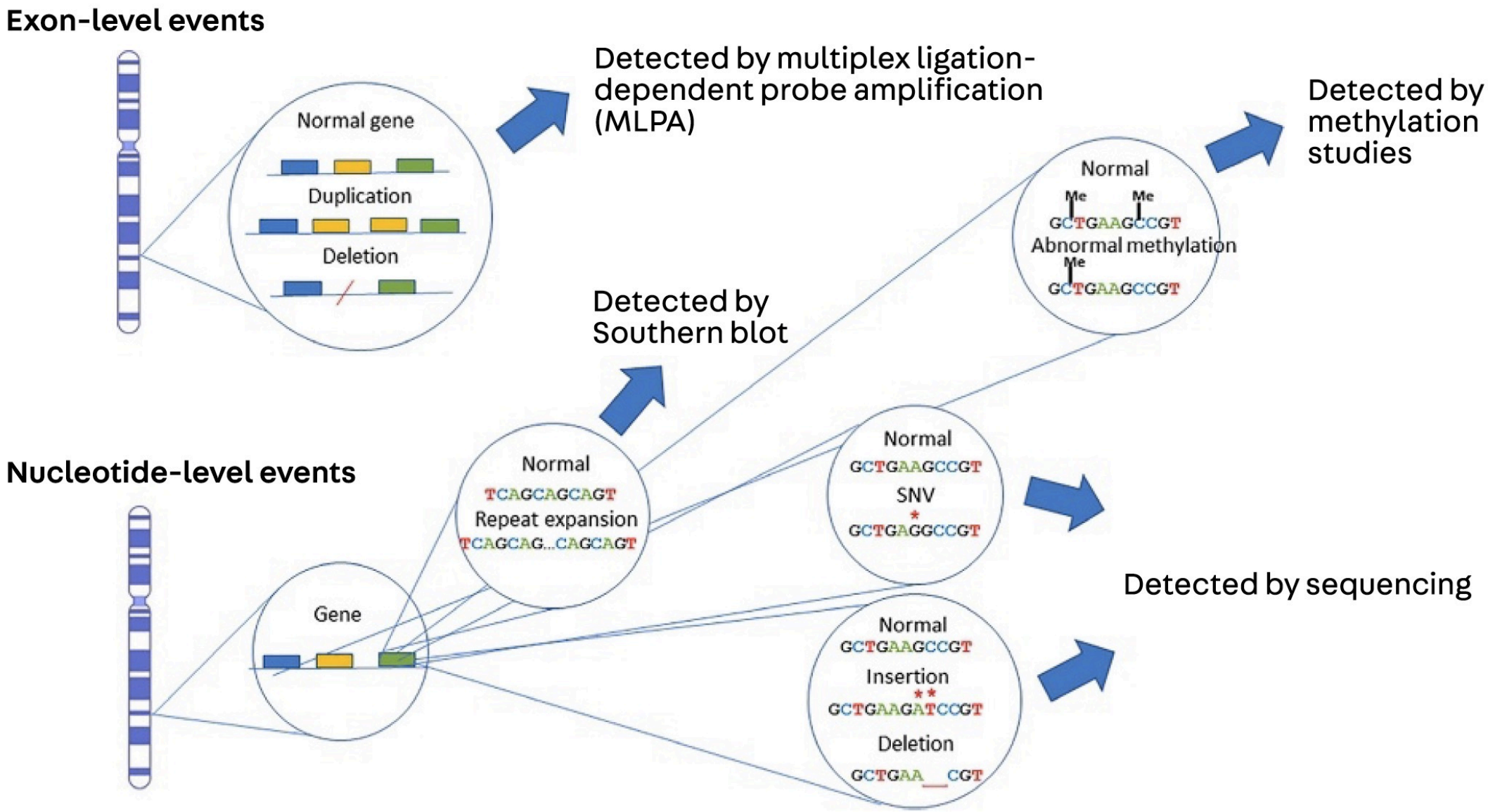




Chromosome Disorders Associated with Epilepsy

Syndrome	Chromosomal abnormalities	Possible diagnostic clue
Wolf–Hirschhorn syndrome	Del 4p	“Greek-helmet” shaped head, cleft lip & palate
Down syndrome	Trisomy 21	Infantile spasms, focal seizures, typical facies
Ring chromosome 20	r20	Nonconvulsive seizures, no dysmorphic features
Inversion duplication 15 syndrome (Tetrasomy 15q)	inv dup(15) or idic(15)	LGS
Angelman syndrome	del(15)q11-q13	“Happy puppet,” characteristic EEG
Miller-Dieker syndrome	LIS1 gene	Classic lissencephaly, typical facial features
Fragile X syndrome	FMR expansion	Macrocephaly, macro-orchidism

Genetic Variability at the Gene Level



Silveira-Moriyama L, Continuum 2018

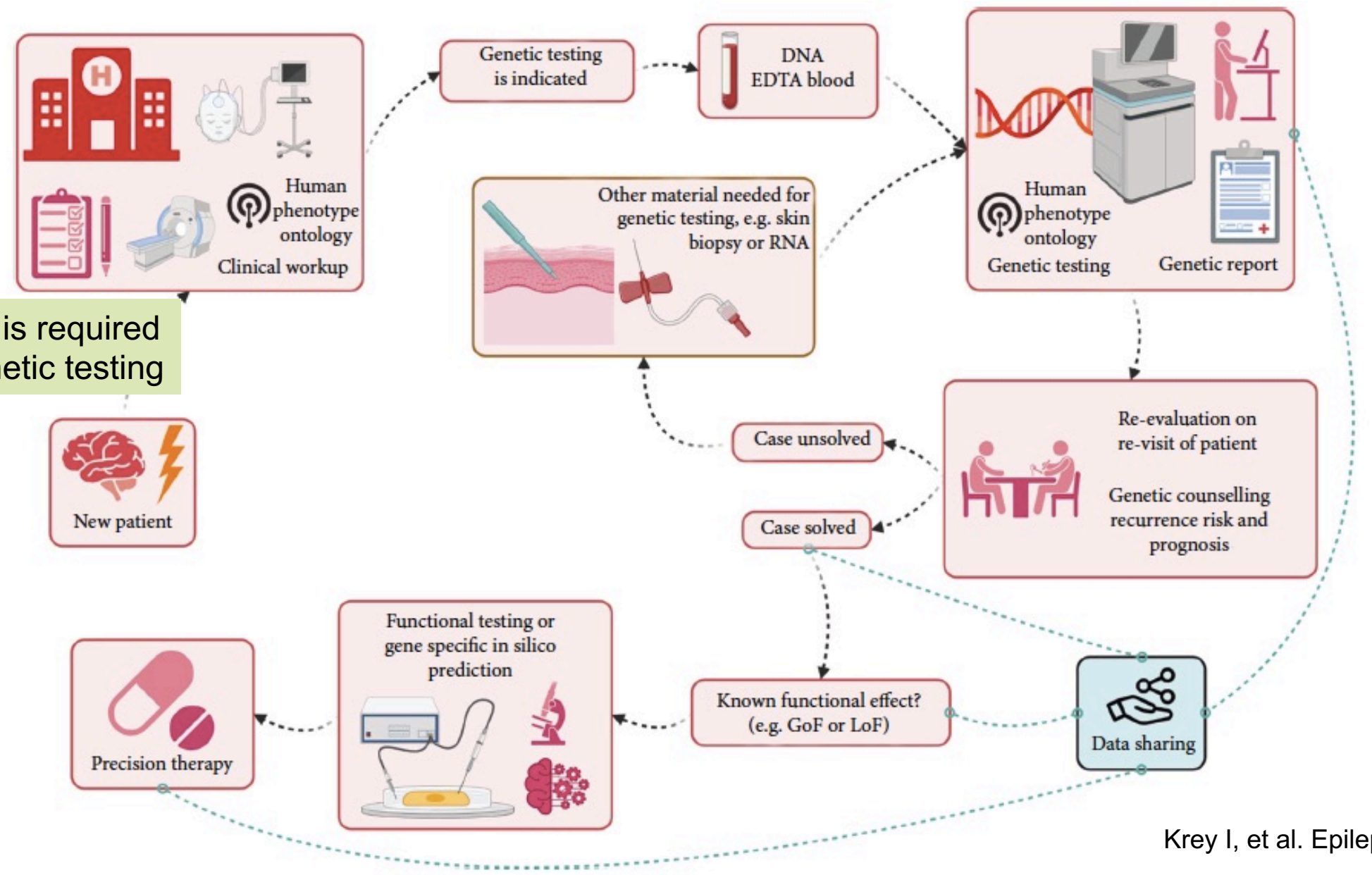
Genetic Testing Methods

- Karyotyping
- Chromosomal microarray (CMA)
- Repeat expansion disorders (e.g. Fragile X, Familial adult myoclonic epilepsy)
- Methylation analysis
- Sanger sequencing
- Next-generation sequencing (NGS)
  - Epilepsy panel sequencing
  - Whole exome sequencing (WES)
  - Whole genome sequencing (WGS)

Angelman Syndrome VS Rett Syndrome

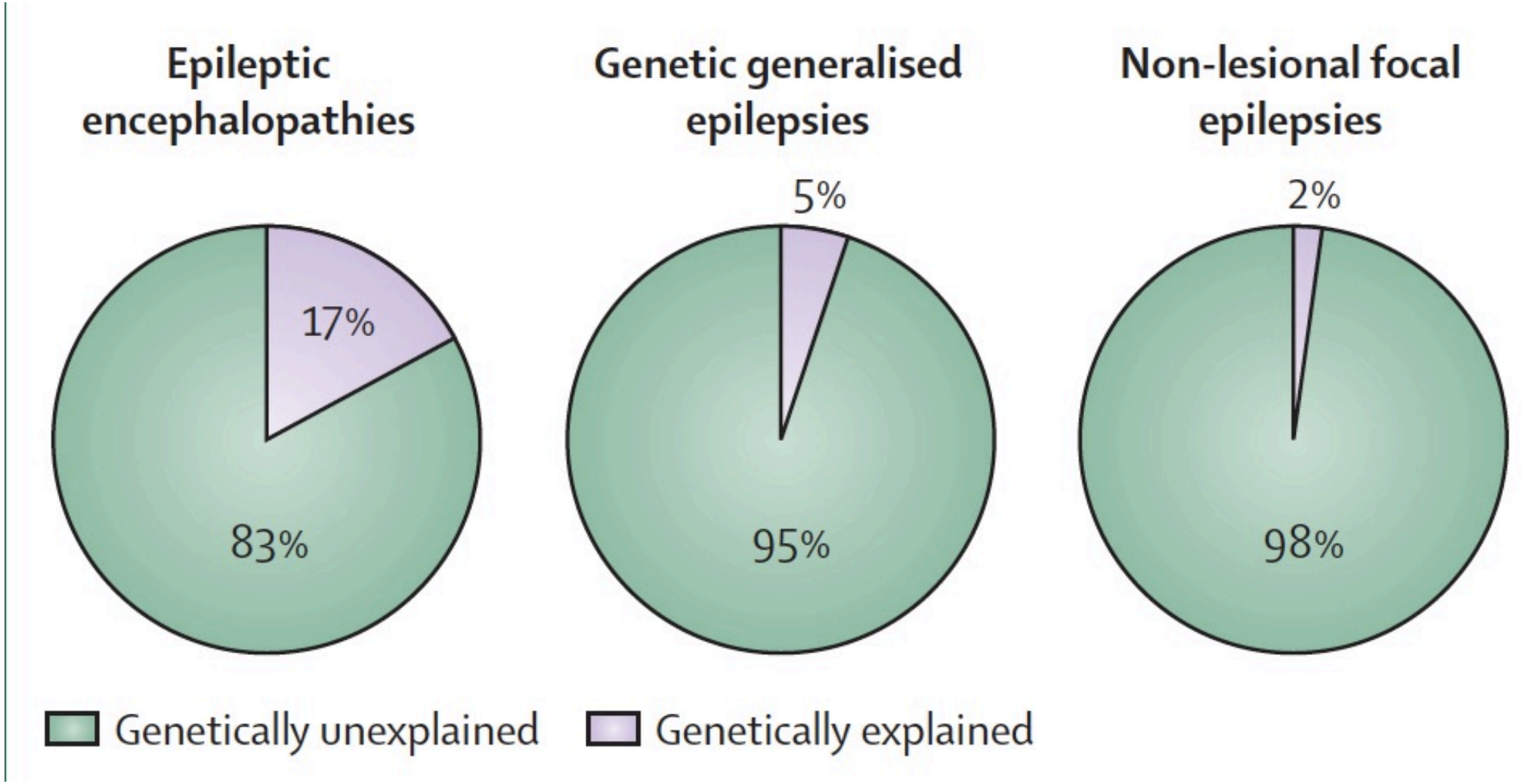
	Angelman	Rett
Gender	M & F	F
Developmental	Delay	Regression
Autistic	Yes	Yes
Head Circumference	Acquired microcephaly	Acquired microcephaly
Typical feature	Jerky & ataxic movement, laughter	Stereotype hand movement
Seizure	Common	Common
Genetic testing	Methylation test	MECP2 gene

Workflow of Genetic Testing



Krey I, et al. Epileptic Disord 2022

Proportion of Genetically Explained Epilepsy



Likelihood of identifying a genetic cause decreases with increasing age at onset of the epilepsy

EpiPM Consortium, Lancet Neurol 2015

Diagnostic Yield

Genetic test	Yield
Chromosomal analysis	Very low
Sanger sequencing	Very low, nearly obsolete
Chromosomal microarray (CMA)	5-15%
Epilepsy-based gene panels	Up to 25%
Whole-exome sequencing/Trio WES	Up to 45%
Whole-genome sequencing/Trio WGS	Up to 48%

Krev I, Epileptic Disord 2022

Interpretation of Genetic Testing Results

- Pathogenic
- Likel pathogenic
- Variant of uncertain significance (VUS)
- Likely benign
- Benign

Richards S, ACMG, Genet Med 2015

GLUT1DS

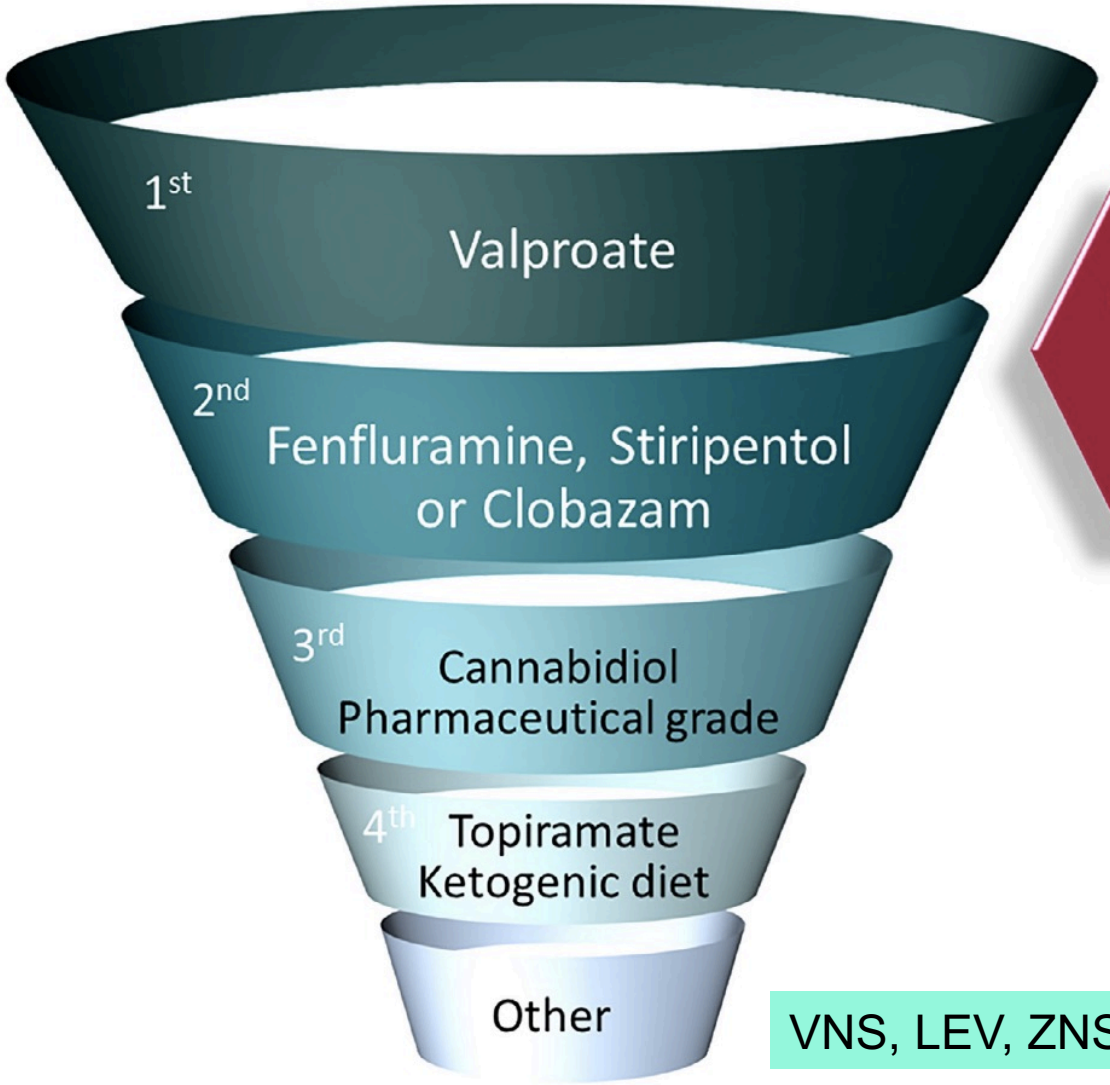
- Cerebral “energy crisis”
- Symptoms develop in an age-specific pattern
- Infancy
  - Early onset absence epilepsy (< 4 oyo), Myoclonic-atonic seizures
  - Paroxysmal eye-head movement
- Movement disorders: paroxysmal or persistent
  - Ataxia, spastic, dystonia
- Acquired microcephaly and cogntive impairment
- LP shows hypoglycorrachia (< 40 mg/dL)
- SLC2A1 mutation or deletion/duplication
- Early ketogenic diet treatment: better intellectual outcomes

Klepper J, et al. Epilepsia Open 2020

Dravet Syndrome

- Normal growth and development as infants
- Seizures present in the first year of life
  - Initially, GTC often prolonged, associated with fever
  - Prolonged hemiclonic seizures
- Evolution to myoclonic seizures, atypical absence seizures, generalized tonic-clonic seizures with/without fever, and complex partial seizures, usually with secondary generalization
- Concomitant psychomotor decline
- Unfavorable outcome due to ongoing seizures
- Genetic etiology: 70%-80% have **SCN1A** mutations

Treatment Algorithm for Dravet Syndrome



AVOID
Carbamazepine,
Oxcarbazepine
Lamotrigine,
Phenytoin**

PHT may be helpful for SE

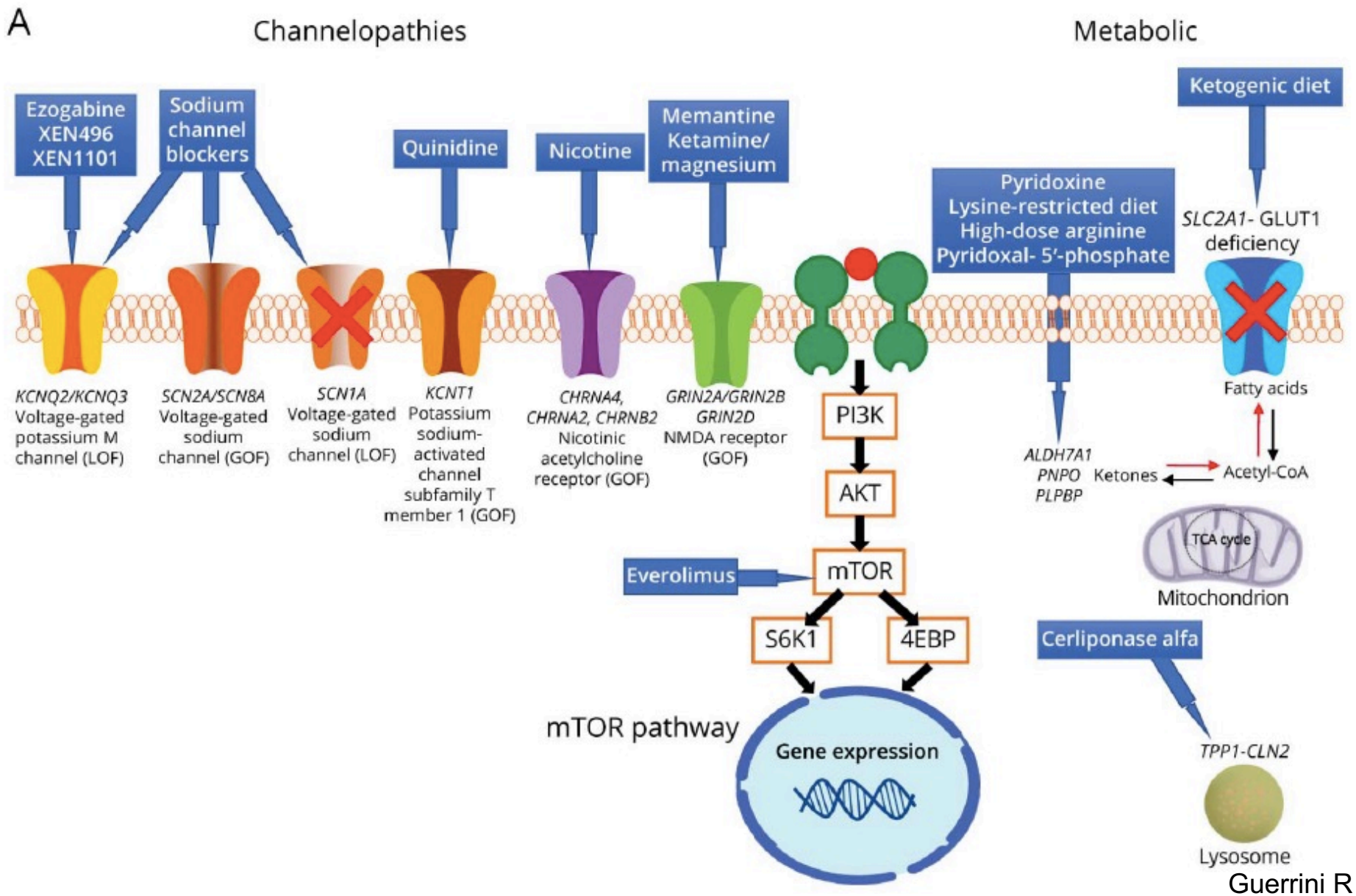
VNS, LEV, ZNS, CNZ

Wirrell EC, et al. Epilepsia 2022

Examples of Precision Therapies

Gene	Potential therapy
ALDH7A1, PNPO, PROSC	Pyridoxine, Pyridoxal-5-phosphate
CAD	Uridine
CDKL5	Ganaloxone
CHRNA4, CHRNAB2, CHRNA2	Nicotiine
GRIN1, GRN2A, GRIN2B, GRIN2D	Memantine, dextrometorphane, ketamine (for LOF), serine (for LOF)
KCNA2	4-aminopyridine
KCNQ2/KCNQ3	Retigabine/ Sodium channel blocker
KCNT1	Quinidine
PRRT2	Carbamazepine
SCN1A **SCN2A, SCN8A**	Loss of function: Avoid sodium channel blocker Gain of function: Sodium channel blocker
SLC2A1	Ketogenic diet
TSC1, TSC2	mTOR inhibitor

Disease Mechanism Assoicated with Genetic Epilepsies



Guerrini R et al. Neurology 2021

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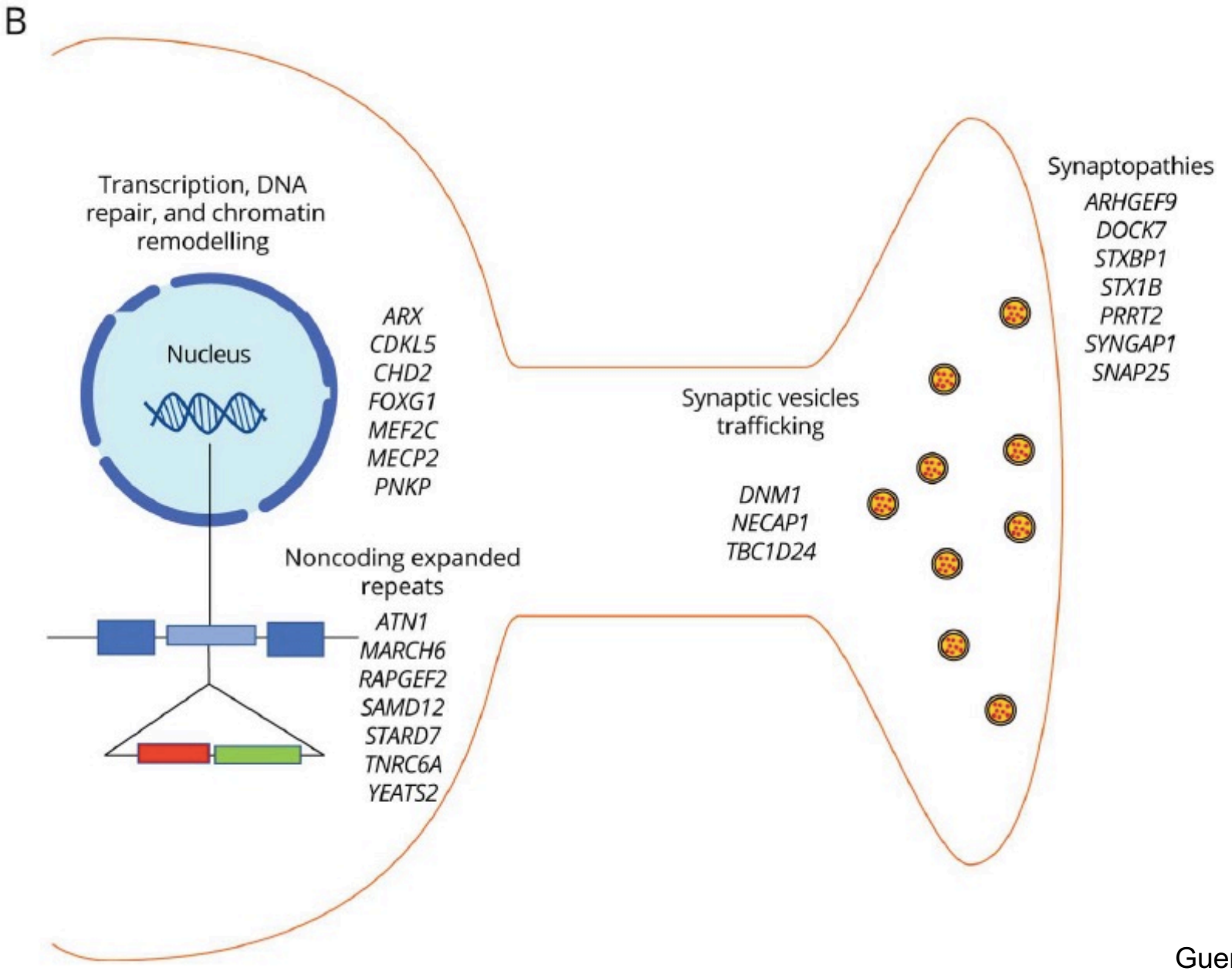

Guerrini R et al. Neurology 2021

Implication on Therapeutic Decision-Making

- 418 patients (377 children, adult 41)
- Changes in clinical management (50%)
  - Add a new medication (22%)
  - Initiate of medication (14%)
  - Referral to a specialist (13%)
  - Vigilance fo subclinical or extraneurological disease (13%)
  - Cessation of medication (12%)

McKnight D, JAMA Neurol 2022

Impact of Childhood Epilepsies

- Danish epilepsy center
- 101/188 (54%) genetically solve cases
- Causative variants: SNVs/indels 82%, CNVs 17%
- 53 of 101 were eligible for precision thearpy
- 32/53 (60%) treatment was adjusted according to genetic findings
- 30/32 (93%) had 50% seizure reduction, 4 became seizure-free
- Everolimus and fenfluramine were the most commonly used

Bayat A, Neurotherapeutics 2022

Impact in Adults with Epilepsy

- Danish epilepsy center (2013-2018)
- 200 adults with 91% had intellectual disability
- 46/200 (23%) found a genetic cause
- SCN1A (36%), KCNT1 (6%), STXBP1 (6%)
- 11/46 (17%) had gene-specific management (SCN1A = 10, one with SLC1A1)
- Improvement of seizure control and cognitive function in 10 patients

Johannesen KM, Epilepsia 2019

Genetic Testing in Epilepsy Recommendation

Recommended in

1. Severe childhood onset epilepsies, particularly DEE
2. Epilepsy with intellectual disability, autism, and/or other comorbidities
3. Progressive myoclonic epilepsies and progressive phenotypes

Considered in

1. Non-acquired focal, drug resistant epilepsy
2. Epilepsy in the setting of malformations of cortical development

Krev I, ILAE Genetics Commission, Epileptic Disord 2022

Conclusion

- Genetic testing in epilepsies is a clinically useful tool
- Diagnostic yield is higher in earlier age of onset and DEE
- Genetic findings can be useful for therapeutic decision making in children and adults
- Precision therapies can be employed (in some cases)
- Improve seizure control and quality of life