Epilepsia de cauza genetica -provocare de diagnostic si tratament-

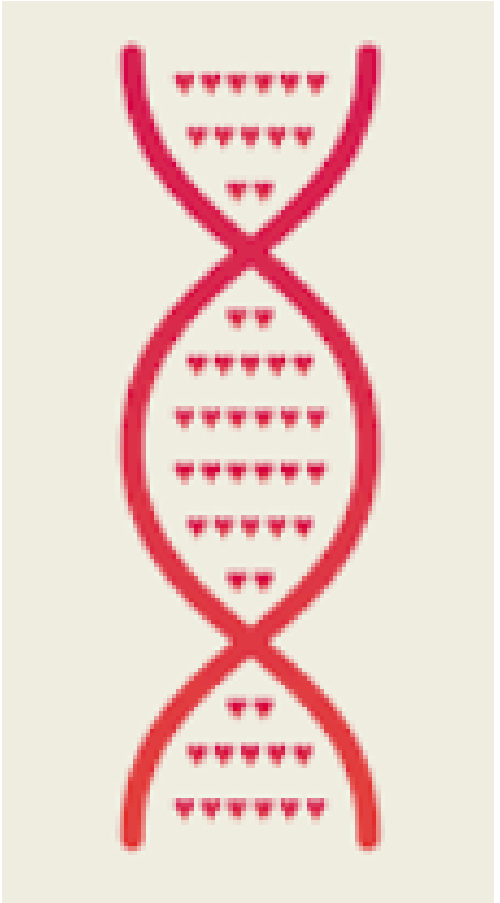
Dr. Eugenia Roza, Dr. Smaranda Niță, Dr. Diana Epure,
Șef lucrări Dr. Raluca Ioana Teleanu

Epilepsie genetica – 30% din epilepsii

Encefalopatie epileptica determinata genetic-complexa, frecvent progresiva (crizele agraveaza tabloul clinic)

Rezultat direct – defect genetic cunoscut/presupus – cromozomial/molecular

CRIZELE EPILEPTICE – rol central



- Genetic ≠ mostenit – mutatii de novo frecvent
- Factori epigenetici !

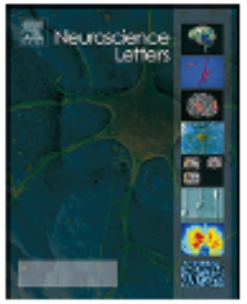
- Mutatii – mare parte – afectarea canalelor ionice → hiperexcitabilitate neuronala/ reducerea mecanismelor inhibitorii → crize epileptice

- Mutatii – gene care codifica proteine – asociate cu epilepsie/ encefalopatii epileptice.

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet



Review article

Recent advances in epilepsy genetics

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Progrese importante in domeniul epilepsiilor genetice

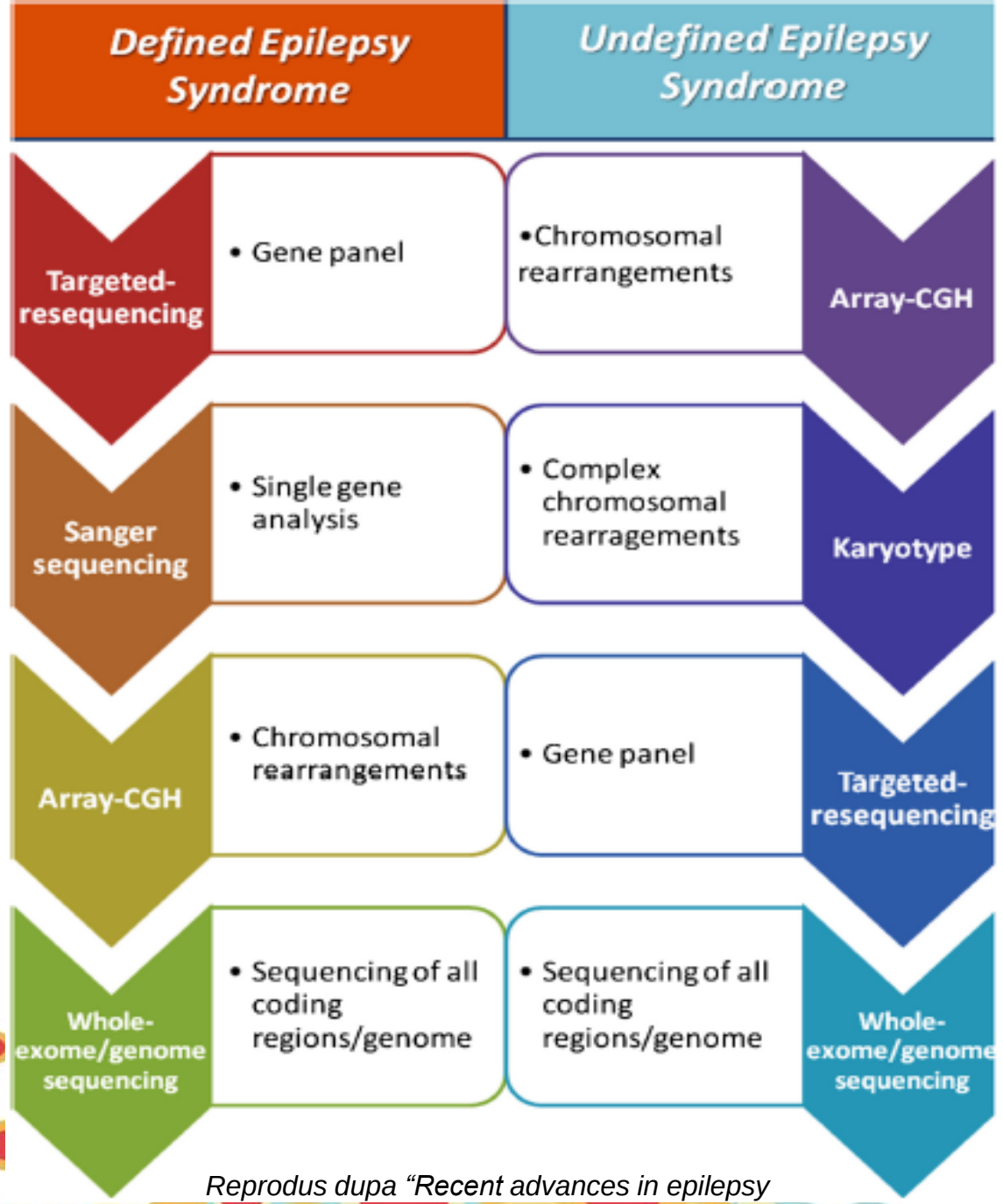
Teste genetice utile

CGH- Array

Next Generation Sequencing → paneluri epilepsie

WES

WGS



Reprodus dupa "Recent advances in epilepsy genetics" , Neuroscience letters 2017

Array CGH

- Metoda de prima linie:
  - Epilepsie + dismorfism facial, anomalii congenitale, afectiuni neuropsihiatrice
  - Permite detectia microdeletiilor si microduplicatiilor genomice (invizibile la cariotipare)
  - Defineste exact regiunea genomica modificata → genele de la acel nivel→corelare mai buna genotip-fenotip
  - Rezultatele- interpretare atenta – semnificatie incerta a variantelor numarului de copii.

Alte tehnici de citogenetica

- FISH – suspiciune de sd de microdeletie/microduplicatie , caracterizarea mai eficienta a anomaliilor cromozomiale
- MLPA- deletii/duplicatii intragenice (ex SCN1A, CDKL5 negative pe aCGH)

Next Generation Sequencing

- Permite secventierea mai multor gene
- Rapid
- secventiere simultana – fragmente ADN +++:
- Exonii unor gene anume → PANELURI
- Intregul exom

WES/ WGS

- Secventiere exom – codifica proteine – 20.000 gene
- Analiza WES:
  - Compara variantele gasite cu variantele non-patogenice din populatia generala
  - De novo/nu – parintii
  - Homozigot/ heterozigot compus
- Util DAR – descoperiri incidentale – interpretarea complicata

Implicatiile testarii genetice in managementul pacientului

- Consiliere genetica
- Decizie terapeutica
- Evolutie – progresiva/ non-progresiva – calitatea vietii pacientului, costuri (investigatii inutile)
- Colaborare buna genetician- neurolog pediatru – esentiala

Ce lipseste? → UNITATE/ UNIFORMITATE

Consens → algoritmi de diagnostic

- Cand testam?
- Cum alegem metoda de testare?
- Implicatii clinice si practice?

Table 1
Diagnostic tests for epilepsy patients.

Diagnostic test	Description	When to use it
Array-CGH	Identify single nucleotide polymorphisms (SNP arrays) or to determine chromosomal rearrangements submicroscopic (array-CGH) as CNVs.	Epilepsy with developmental delay, dysmorphism, ASD
Single gene sequencing	Detects changes in the gene and if it causes amino acid alterations	Suspected single-gene defect (e.g. SLC2A1 in Glut-1 deficiency)
Duplication deletion of a single gene	CNV of a single gene	Suspicious of a single gene defect when sequencing is inconclusive
Research of a specific mutation	Sequencing of a specific mutation	On parents to understand if an unknown mutation is pathological
Targeted-resequencing	Sequencing and duplication/deletion research of a gene panel for a specific disease	disease with more genes involved
Fluorescent in situ hybridization (FISH)	Probes that analyse specific chromosome's portions	Confirmation of a duplication/deletion
Karyotype	Analysis of all chromosome for big duplication/deletion	Patients with dysmorphism and/or multiorgan dysfunction
Whole-exome and genome sequencing	Sequencing of all DNA only for codifying regions (exons) or all regions (genome)	Suspected genetic aetiology with otherwise normal investigations

Reprodus dupa "Recent advances in epilepsy genetics" , Neuroscience letters 2017

Ce lipseste? → UNITATE/ UNIFORMITATE

Consens:

- Cand testam?
- Cum alegem metoda de testare?
- Implicatii clinice si practice?

“One stop facilities” – centre multidisciplinare interconectate

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Clinical utility of genetic testing in pediatric drug-resistant epilepsy: A pilot study

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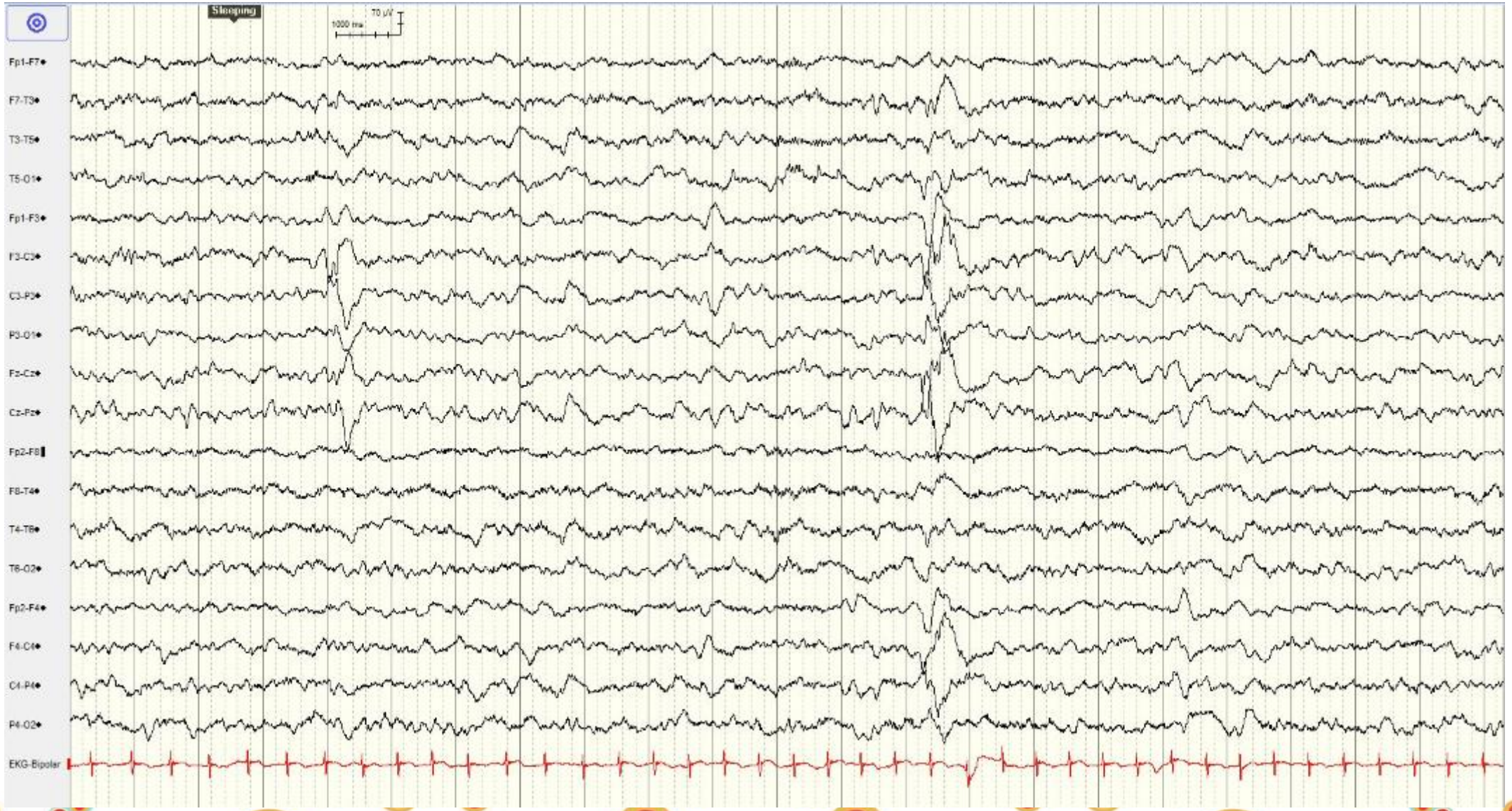
Experienta clinicii de Neurologie Pediatrica a Spitalului Dr. Victor Gomoiu

- Serie de cazuri-

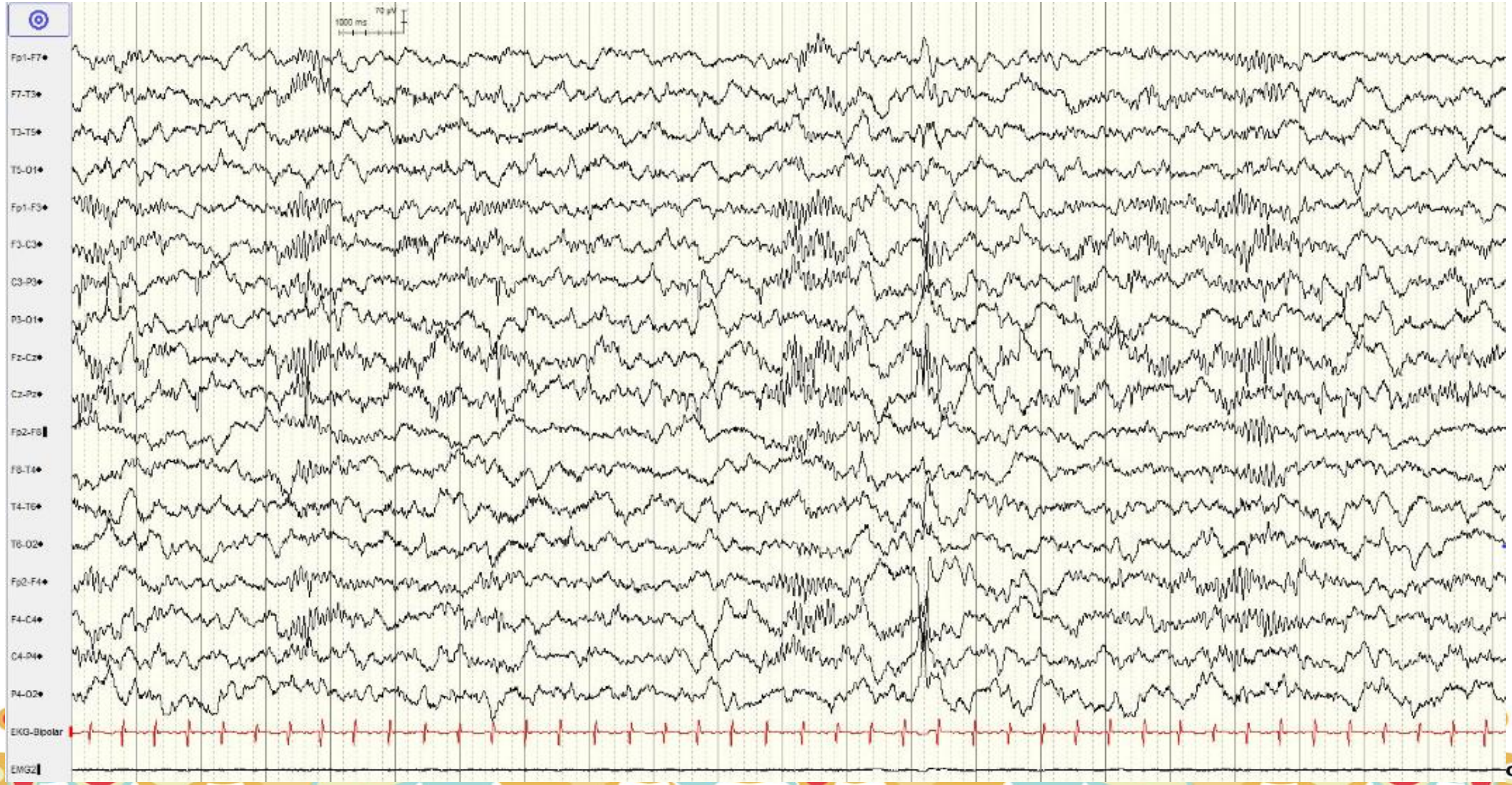
C.L.

- APF nesemnificative
- AHC :
  - mama – convulsii febrile
  - sora – 8 ani – convulsii febrile in perioada de sugar
- Dezvoltare normala motor, intarziere de limbaj expresiv
- Debutul crizelor 1 an 6 l – in context febril, aspect generalizat – se repeta la aproximativ 3 luni
- Ulterior- o criza in afebrilitate, manifestari paroxistice cu cadere de la propriul nivel- origine incerta
- Tratament – Nitrazepam, Depakine

EEG initial 1 an 6 luni



EEG 3 ani 2 luni



C.L.

Dravet?

GEFS+?

→SCN1A negativ

- crize- context febril
- intarziere in dezvoltarea limbajului
- Posibil crize atone?

Panel epilepsie 283 gene→ GRIN2A

Atipic- EEG modificari fruste veghe si somn

P.T.

- APF nesemnificative
- AHC – mama- convulsii febrile
- Clinic- comportament hiperkinetic,inabilitate motorie

Prima criza – 1an 6 luni – generalizata, afebrilitate

1a7l- 6 crize in context febril la 1-2 zile distanta → spital de urgenta- Fenitoina → atacuri distonice

Apoi Fenobarbital + VPA → continua sa prezinte crize

EEG la acel moment- traseu lent → encefalita? – infirmata

P.T

- Parintii cer retragere VPA
- Introducere Carbamazepina – fara crize 5 luni
- Second opinion Spania - ++ Carba (nivel seric suboptimal) → reapar crizele – clustere de 13-30 crize/ zi

→Spital de urgenta – ATI- +++ Carba,Acetazolamida, antibioterapie→ fara crize 2 zile

→ reapar , aprox 30/zi → LEV

P.T.

Substrat genetic?

Dravet?→ SCN1A negativ

Panel epilepsie 283 gene→ PCDH19

Crize in cluster, febril/afebril

Agravate de CBZ

Tulburare comportament

Viitor – testare familie

V.N.

- APF si AHC nesemnificative

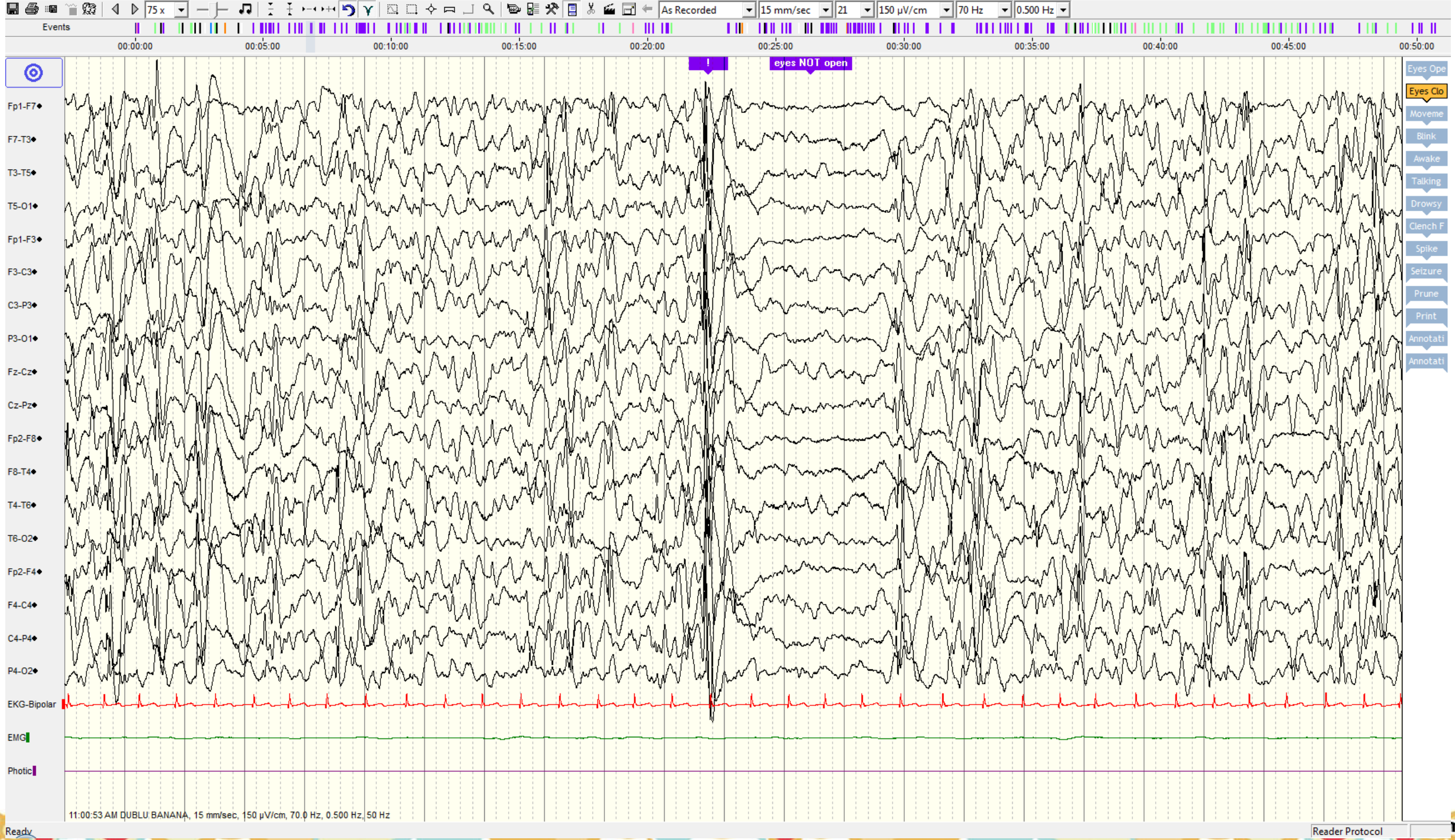
Neurologic- intarziere severa in dezvoltarea neuro-psiho-motorie, hipotonie, bruxism, dismorfism facial usor

Debutul crizelor la o luna- spasme in flexie

Diverse scheme de tratament

Crizele → ulterior polimorfe:

- Spasme la trezire
- TCG din somn
- Evolutie buna pe VPA + Zonisamida + Trileptal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F7-T3
T3-T5
T5-O1
Fp1-F3
F3-C3
C3-P3
P3-O1
Fz-Cz
Cz-Pz
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp2-F4
F4-C4
C4-P4
P4-O2
EKG-Bipolar
EMG
Photic
Eyes Ope
Eyes Clo
Moveme
Blink
Awake
Talking
Drowsy
Clench F
Spike
Seizure
Prune
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Ready
Reader Protocol

V.N.

Encefalopatie epileptica

Etiologie metabolica/ genetica?

Metabolic- fara anomalii

Imagistica cerebrala- normala

Genetic?→ panel 91 gene encefalopatii epileptice → CDKL5

Crize in prima luna de viata

Intarziere severa in dezvoltare

Hipotonie severa

Bruxism

Stereotipii

Registrul CDKL5 Australia

Fig. 1 – The girl with a mutation in the CDKL5 gene had a low hair line, marked ligamentous laxity, and dysmorphic facial appearance, including hypertelorism, a long philtrum, bulbous nose, and carp-like mouth.

Take home message

Nevoia de colaborare multicentrica

Multidisciplinaritate

Consens – protocoale de testare

RETEA!

VA MULTUMESC!