Characteristic phasic evolution of convulsive seizure in *PCDH19*-related epilepsy

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PCDH19-related epilepsy

Epilepsy and mental retardation limited to females (EFMR) (2008, Scheffer)

X-linked protocadherin 19 mutations (2008, Dibbens)

Epileptic encephalopathy caused by mutations of *PCDH19*

- Seizure onset : infantile, early childhood
- Tendency for seizure clustering
- Fever-sensitivity
- Seizure frequency: not so frequent
- Intellectual disability: 2/3
- Psychiatric features such as autism, psychosis

Sheffer *et al*.; 2008, Higurashi *et al*.; 2011, Specchio *et al*.; 2011, Marini *et al*.; 2012, Higurashi *et al*.; 2013

Reported Seizure Types

- Generalized seizures
  - Generalized Tonic Clonic seizurs (GTCS)
  - Absence
  - Myoclonic
  - Tonic
  - Atonic
- Focal seizures

Higurashi *et al*.; 2011, Specchio *et al*.; 2011, Marini *et al*.; 2012, Higurashi *et al*.; 2013

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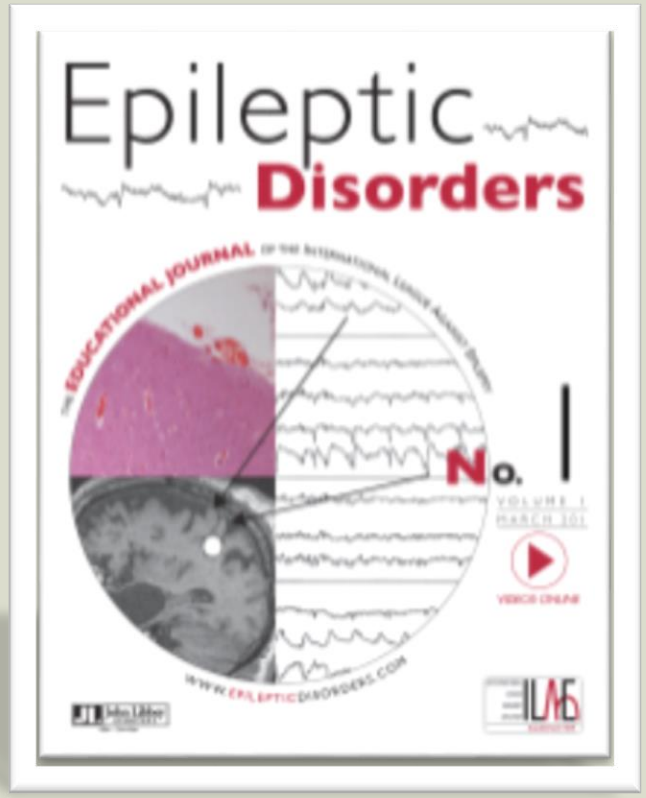

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Characteristic phasic evolution of convulsive seizure in *PCDH19*-related epilepsy*

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Purpose

To elucidate the characteristic features of convulsive seizures associated with

PCDH19 Related Epilepsy.

Methods

- 47 seizures in 5 patients detected on Video EEG
  → 26 convulsive seizures from 3 patients on Video-EEG
- Semiological analysis of convulsive seizures
- Reviewed from medical records
  - family history
  - precipitation by fever
  - frequency and duration of seizures
  - interictal EEG
  - brain imaging
  - Treatments
  - cognitive and behavioural assessments
- Genetic analyses; Fukuoka University

- The patients and their parents agreed to participate in this study and allowed their video to be used.

- The *PCDH19* and *SCN1A* genetic tests were approved by the institutional ethical committee.

Patient 1

- 14-year-old female
- Perinatal; mother suffered severe toxemia
- Past history; unremarkable
- Psychomotor development;

  Normal before, delayed after seizures onset (10m)

  Mild intellectual disability at 11y

  IQ62 (VIQ72,PIQ58)
- MRI/CT; slight diffuse brain atrophy

Family history

Mother (47y)

intellectual disability

Epilepsy

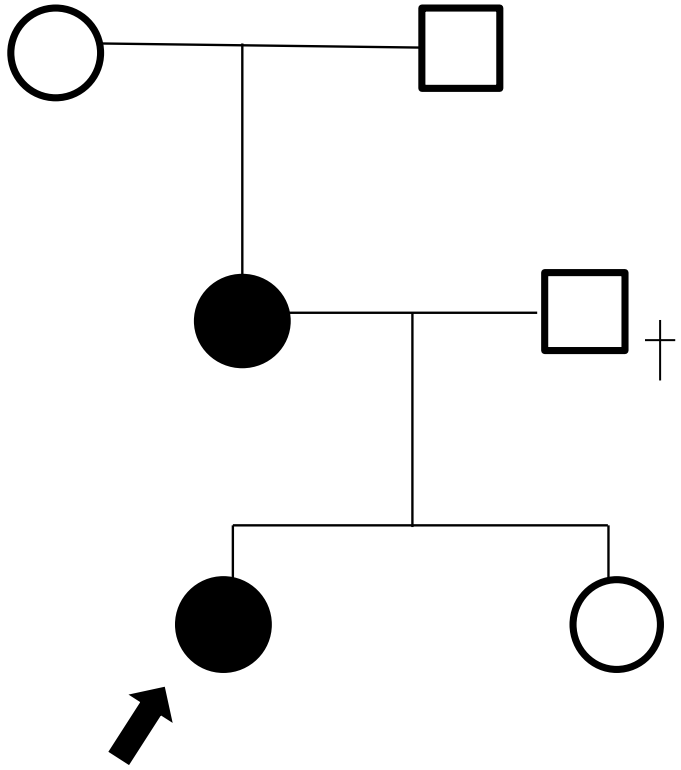
Onset: 5 months

Fever precipitation

Sz type: similar to Patient 1

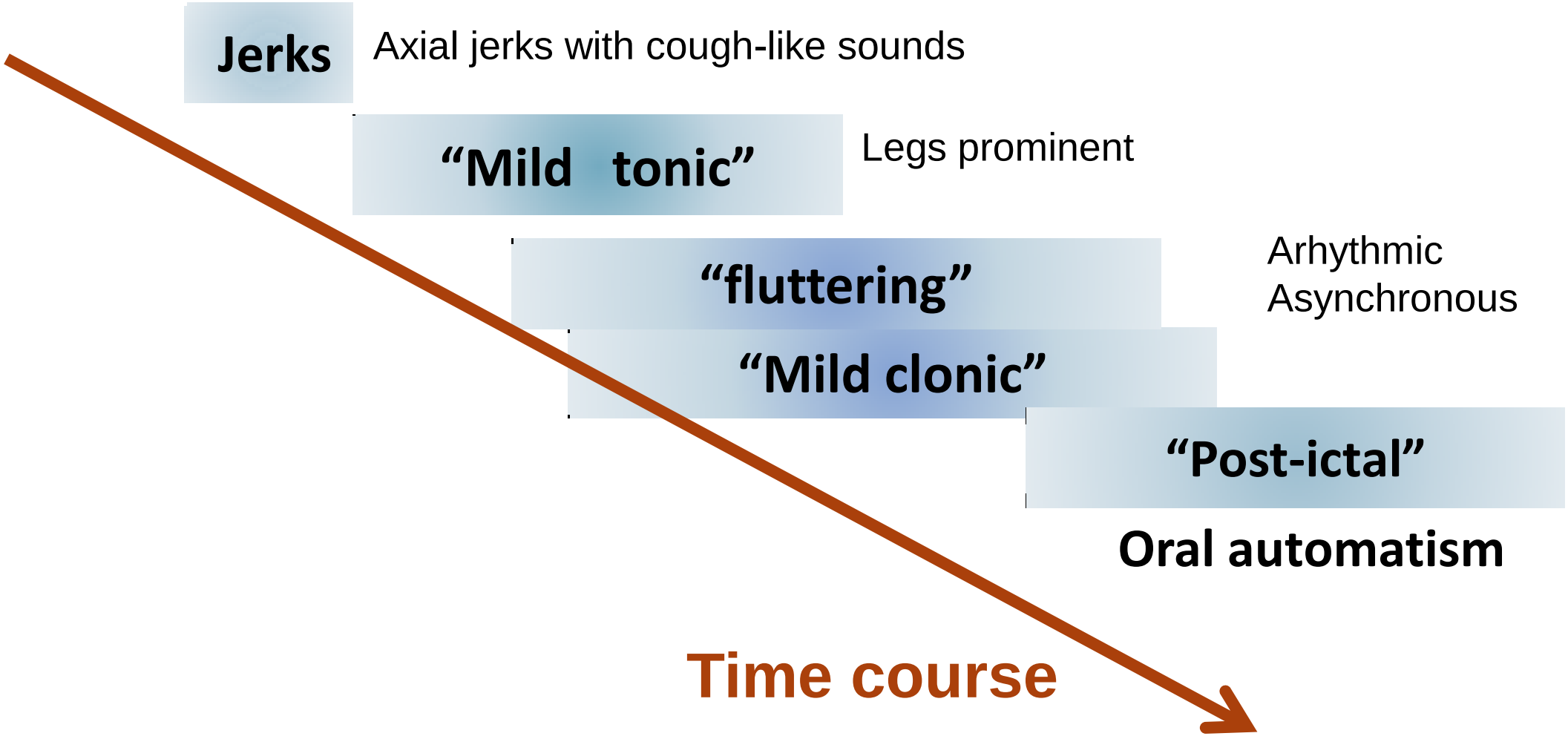
Last seizure: 31y

VPA discontinuation: 45 y



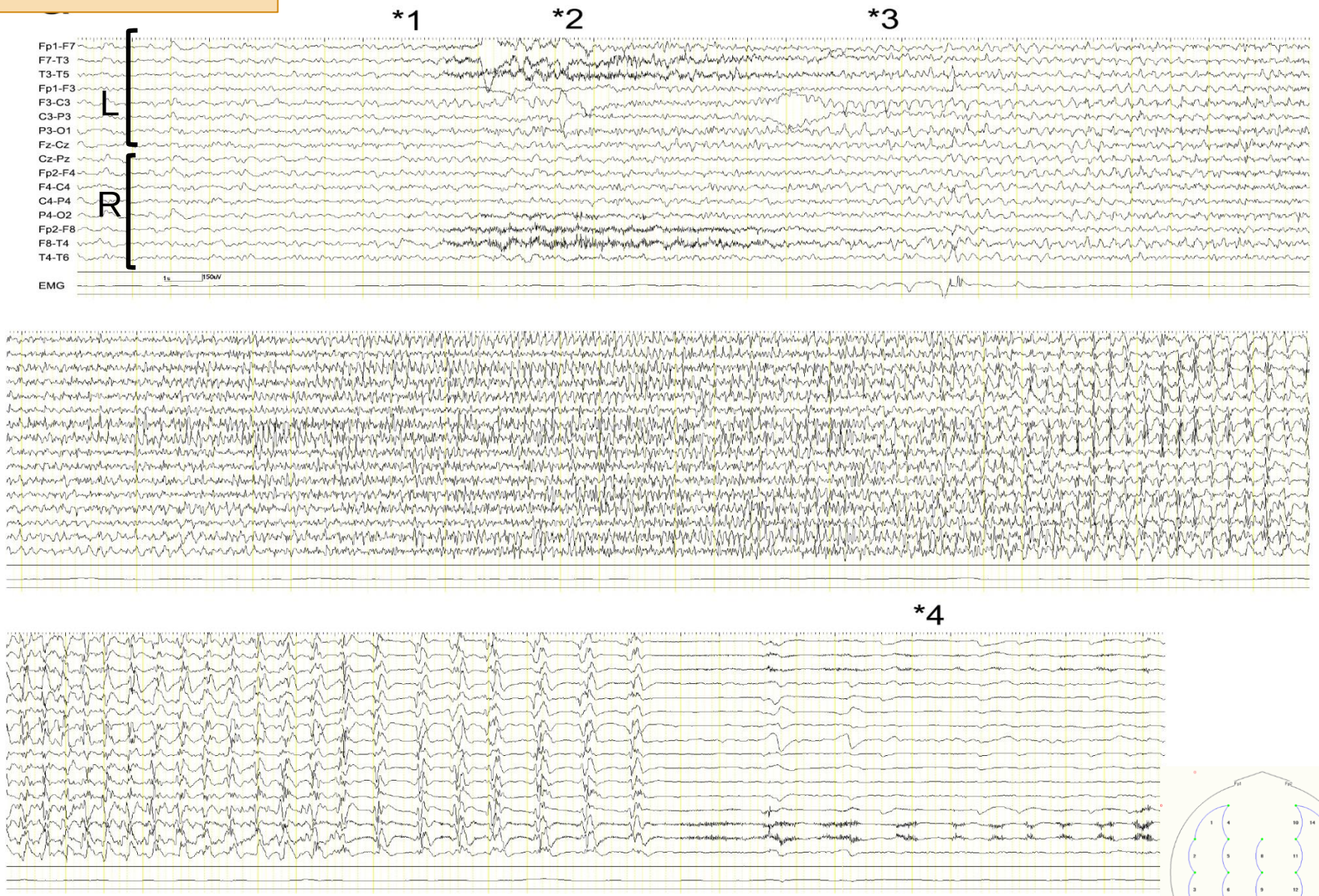
Patient 1 & mother: *PCDH19 missense mutation*
SCN1A testing : negative

Patient 1 (1)


Jerks
Axial jerks with cough-like sounds
“Mild tonic”
Legs prominent
“fluttering”
Arhythmic
Asynchronous
“Mild clonic”
“Post-ictal”
Oral automatism
Time course

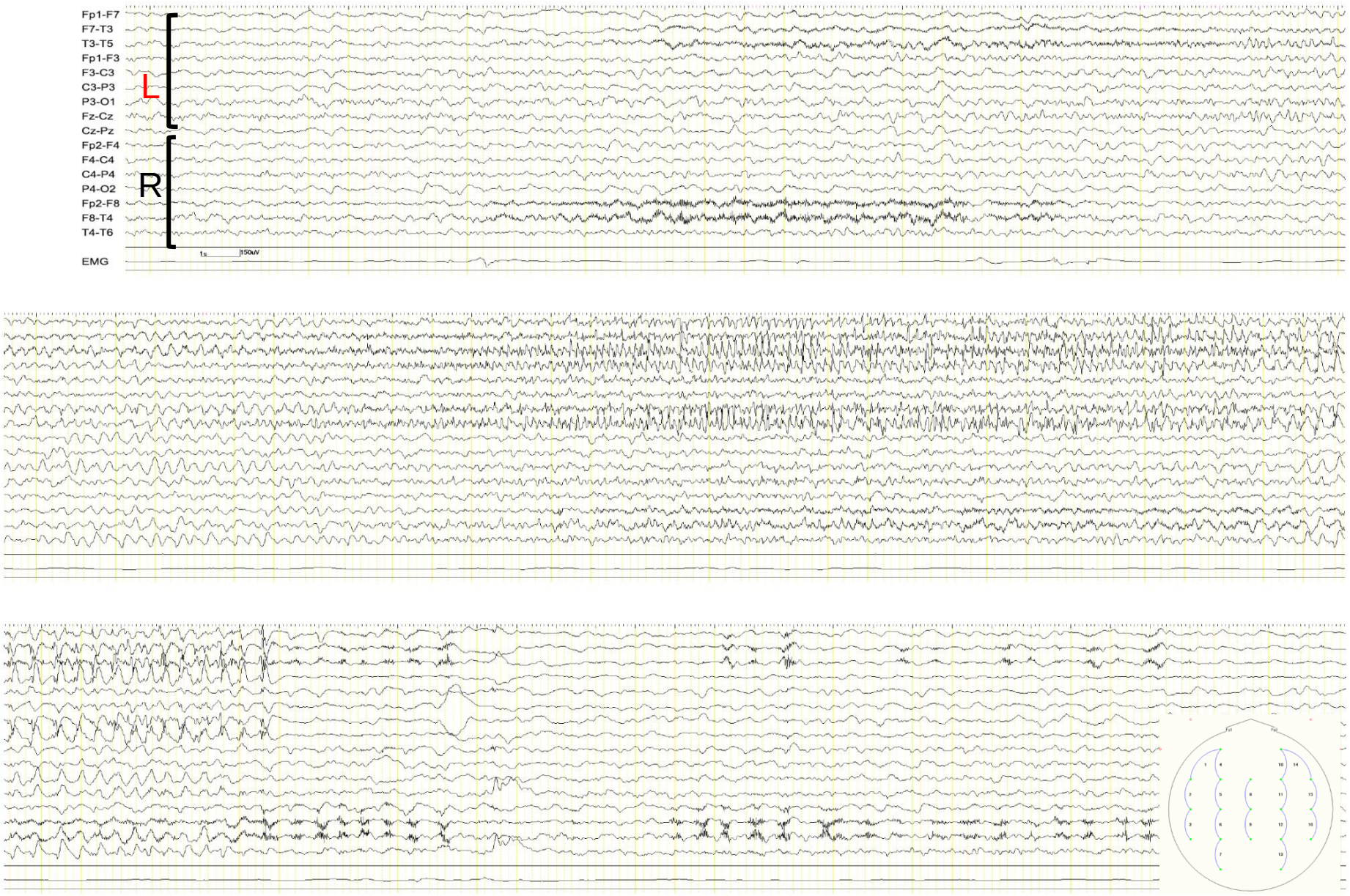
Ictal EEG

Patient 1 (A)



Patient 1 (B)

Ictal EEG



Patient 2

- 6-year-old female
- Perinatal; unremarkable
- Past history; unremarkable
- Development

  Normal before, Delayed after epilepsy onset (6 m)

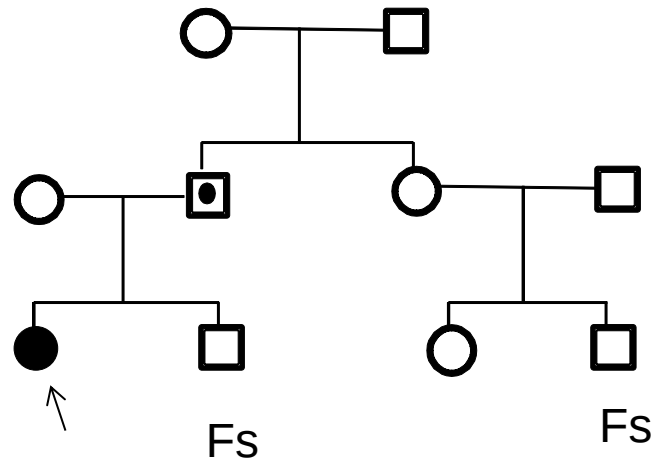
  Intellectual disability and motor development delay; FSIQ 49

  Autism
- MRI/CT; slight diffuse brain atrophy

Family history

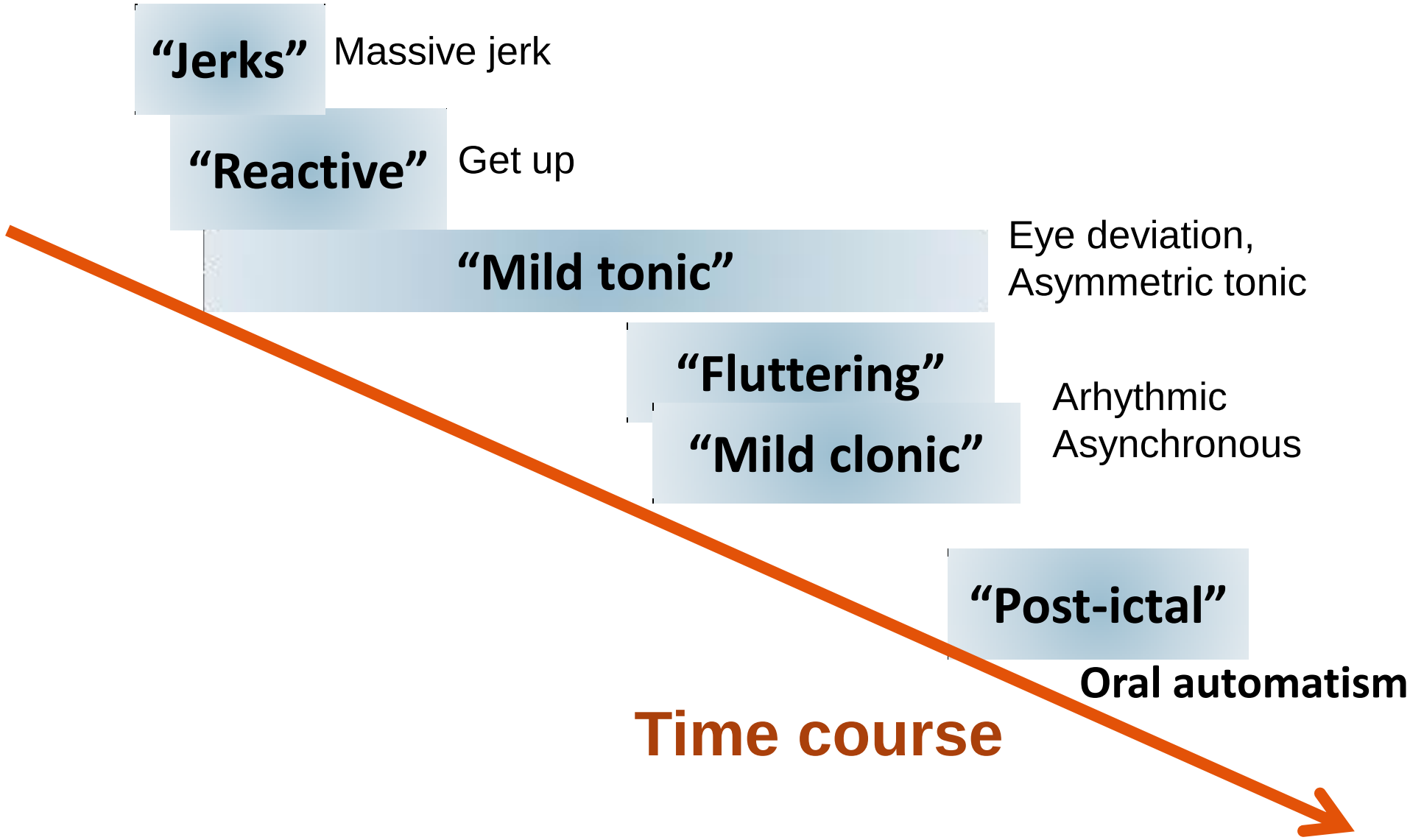
Febrile seizure (single)

- brother
- cousin (father's side)



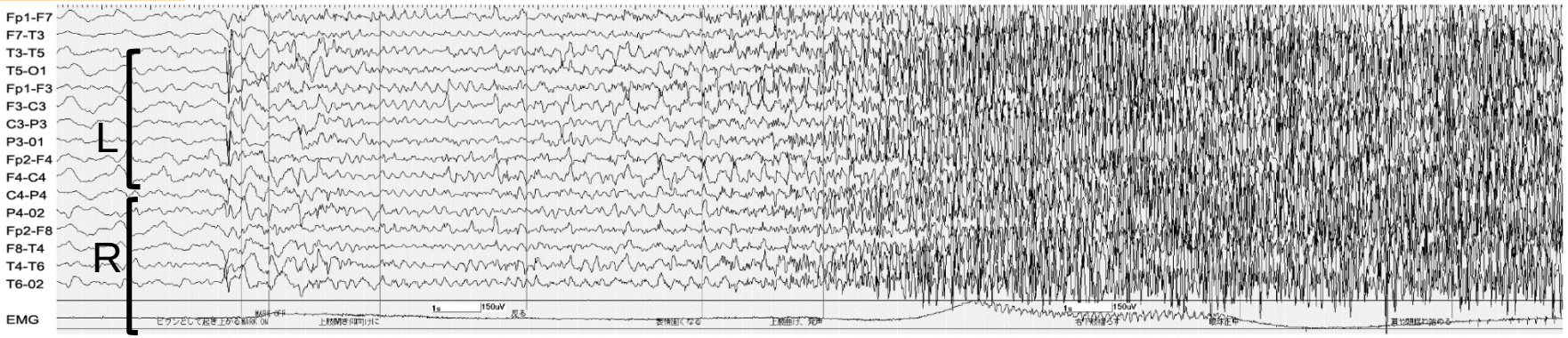
Patient 2 & father： *PCDH19 missense*

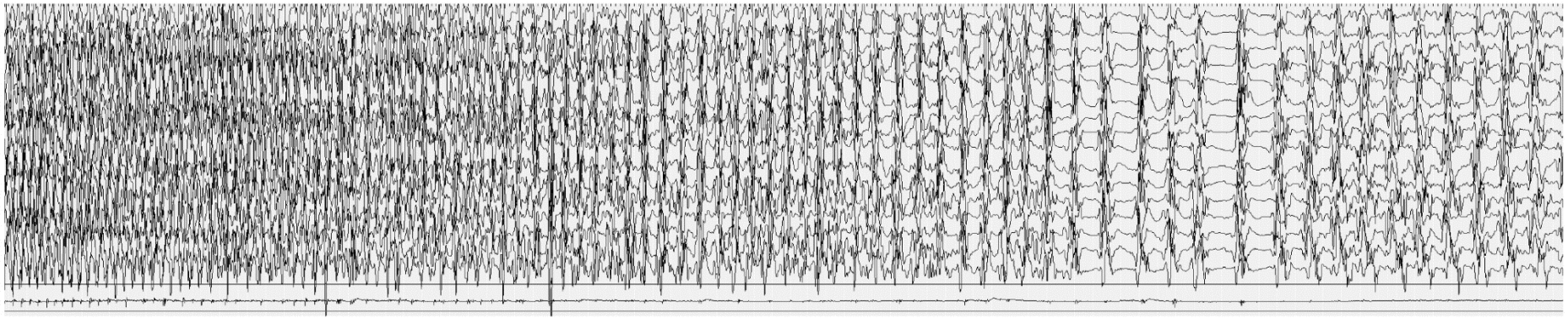
Patient 2 (1)

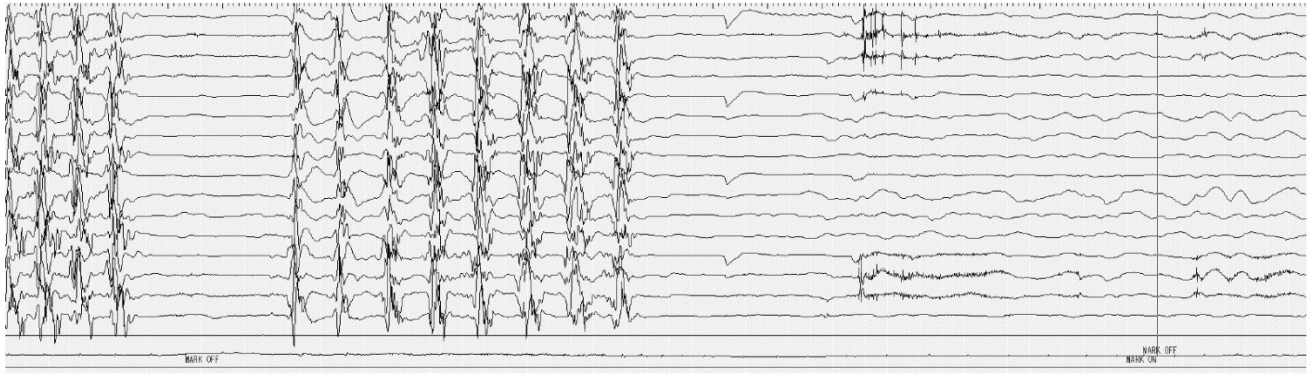

“Jerks”
Massive jerk
“Reactive”
Get up
“Mild tonic”
Eye deviation,
Asymmetric tonic
“Fluttering”
“Mild clonic”
Arhythmic
Asynchronous
“Post-ictal”
Oral automatism
Time course

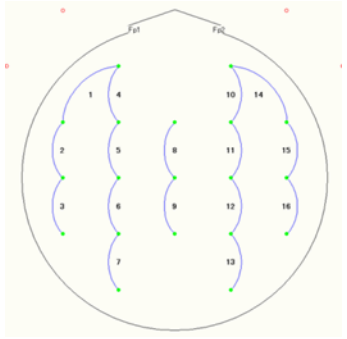
Ictal EEG

Patient 2 (1) *1 *2 *3

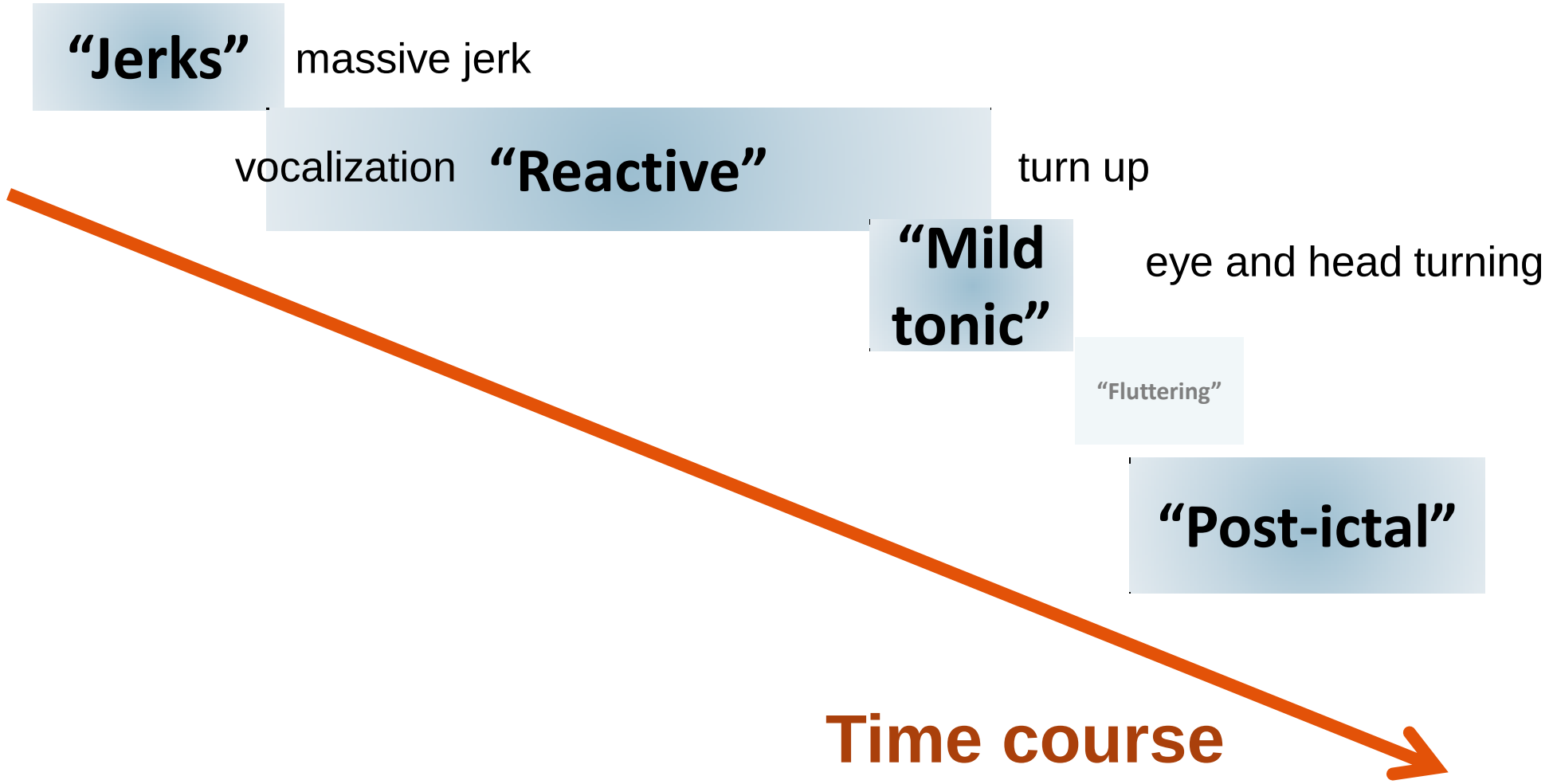






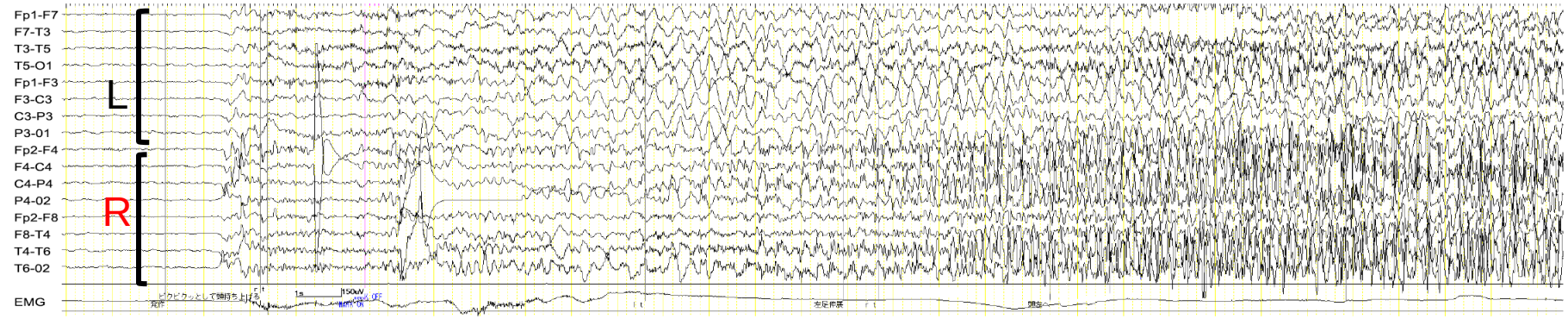


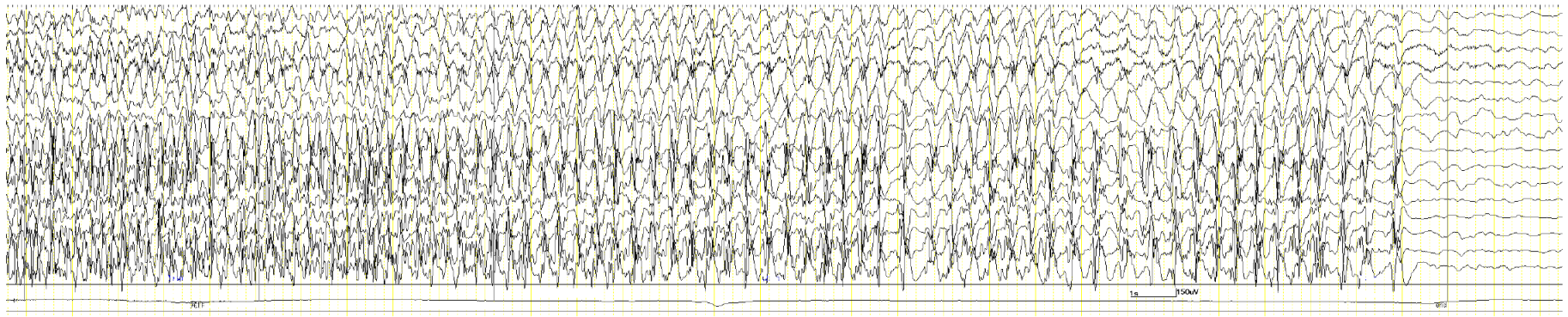
Patient 2 (2)

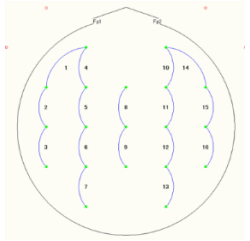

“Jerks”
massive jerk
vocalization
“Reactive”
turn up
“Mild tonic”
eye and head turning
“Fluttering”
“Post-ictal”
Time course

Ictal EEG

Patient 2 (2)







Patient 3

- 3-year-old female
- Perinatal; unremarkable
- Past history; unremarkable
- Development

  Normal before, Delayed after sz onset (9 m)

  Intellectual disability and motor development delay

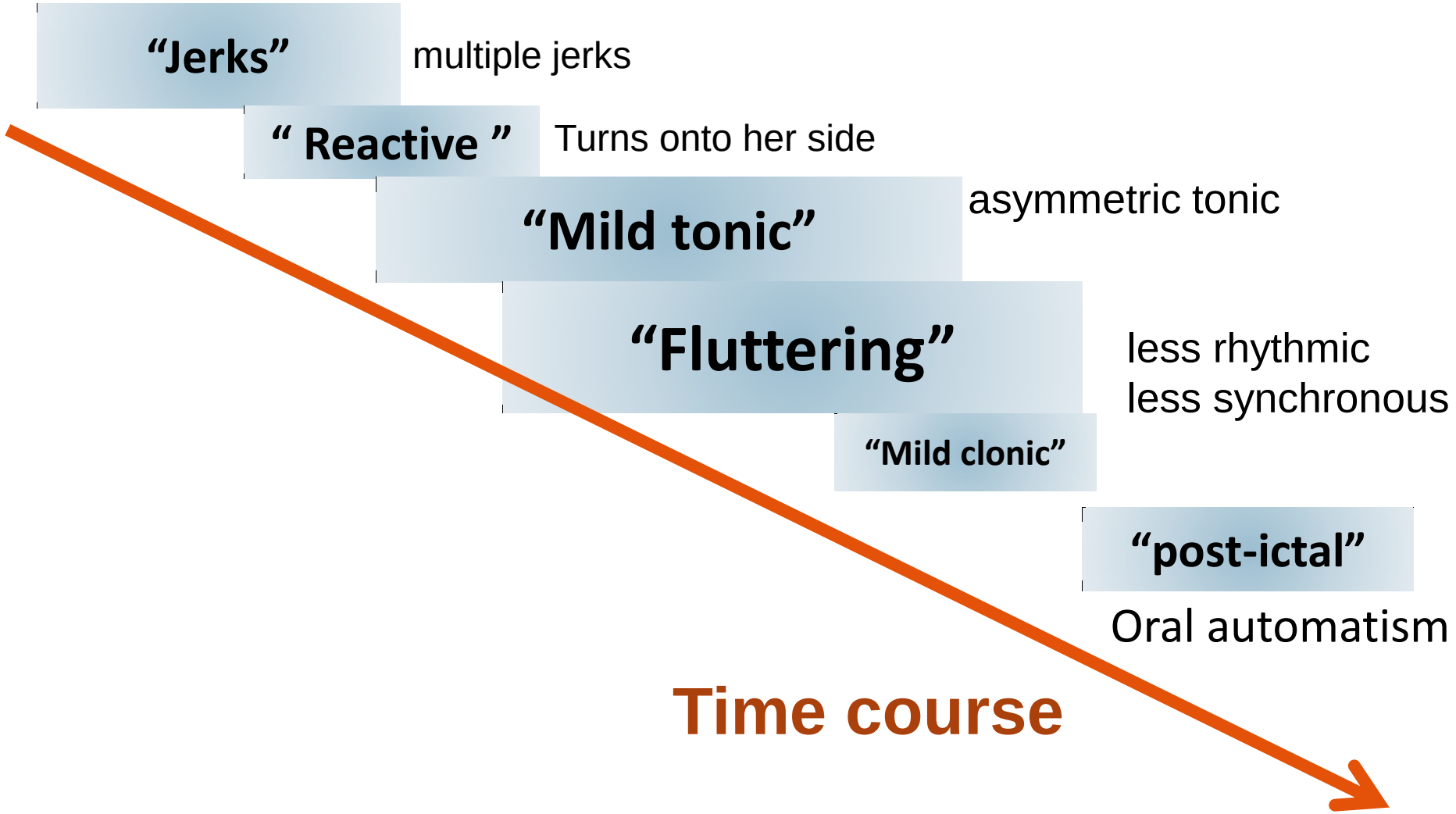
  FSIQ 49
- Autism

Family history

Febrile seizure (single): Aunt (mother’s side)

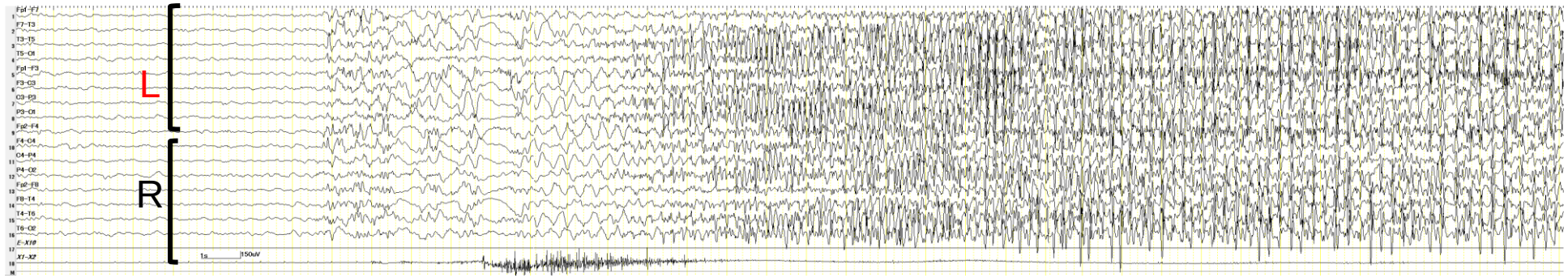
Patient 3 ： *PCDH19 heterozygous whole-gene deletion*

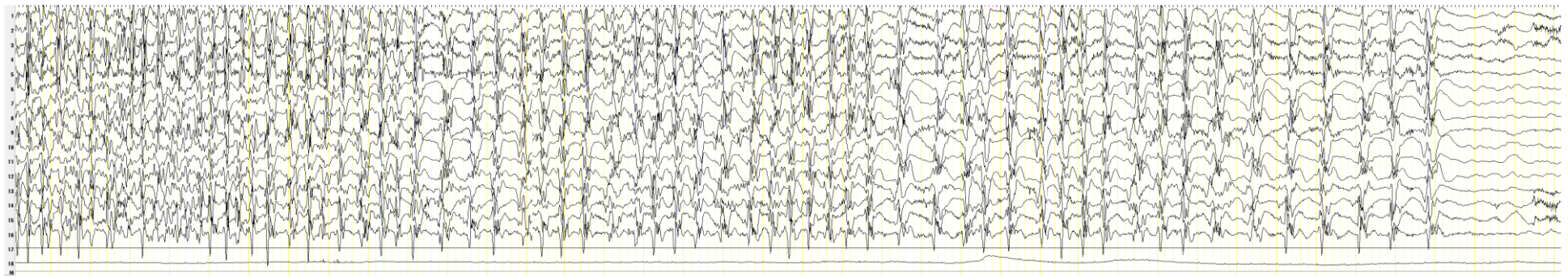
Patient 3

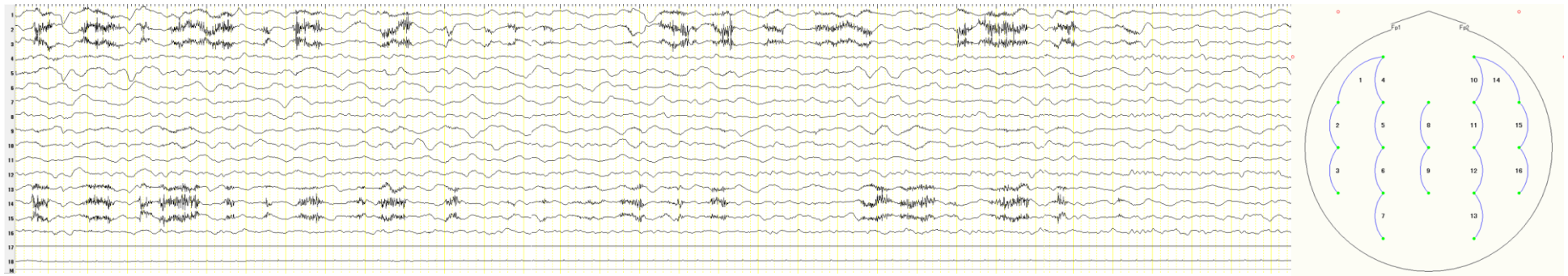

“Jerks”
multiple jerks
“ Reactive ”
Turns onto her side
“Mild tonic”
asymmetric tonic
“Fluttering”
less rhythmic
less synchronous
“Mild clonic”
“post-ictal”
Oral automatism
Time course

Patient 3

Ictal EEG

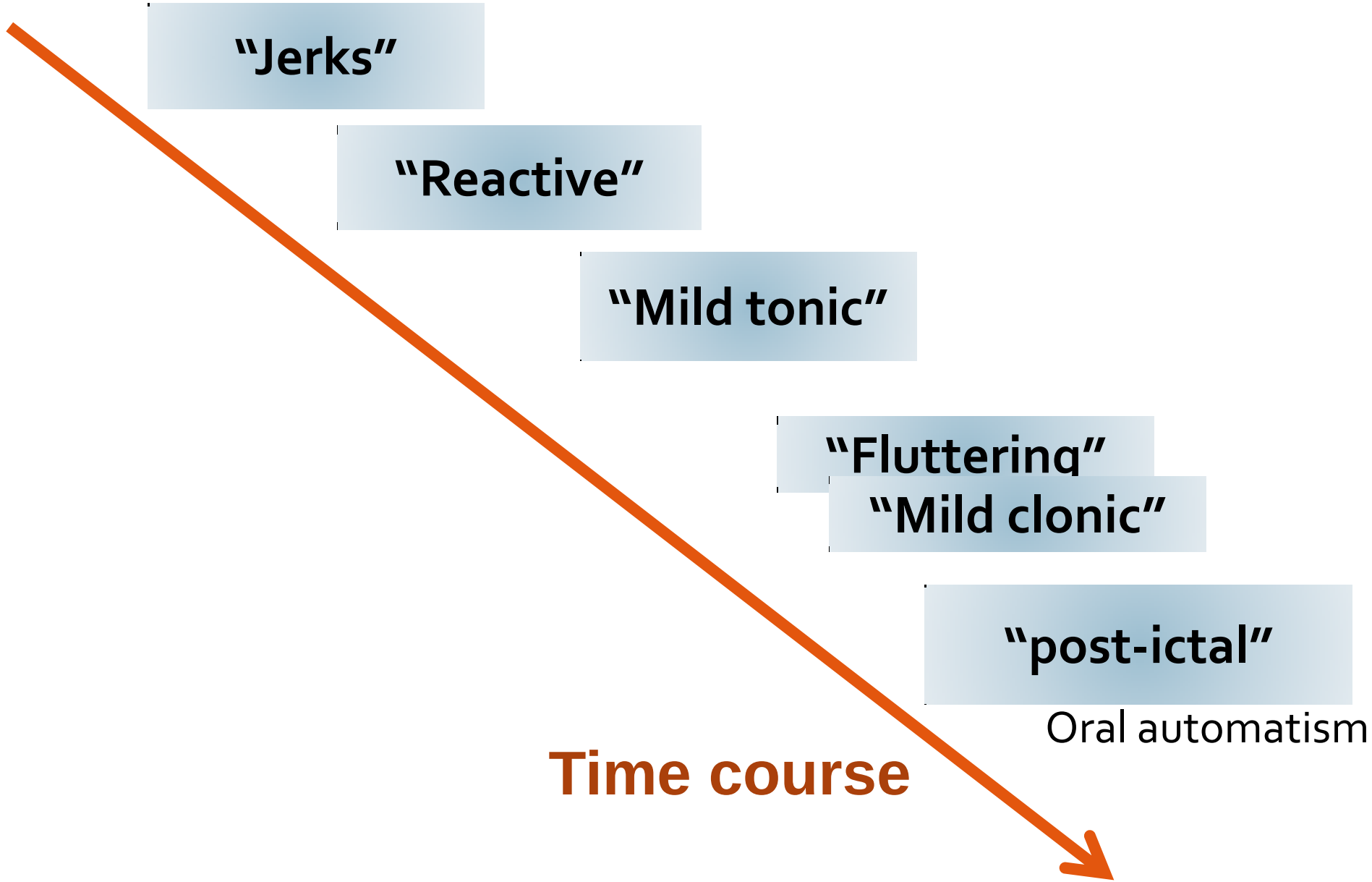






Discussion

Six phases of sequence of seizures



“Jerks”

- axial～limbs
  - cough/gurgling sound (axial jerks)
- singly or repeated irregularly
  - without spikes and waves on EEG

“Reactive”

- “panic” , fearful state
- turn over / sit up
- affective symptoms
- complex gestural automatisms

“Mild tonic”

- less intense
  - reduced involvement of the deltoid muscles
  - Asymmetric
- EEG
  - recruiting fast rhythm
  - from unclear or different foci

“Fluttering” → “Mild clonic”

- Extremities
  - distal prominent
    (fingers, hands)
  - trembles and jerks
  - asymmetric
  - less rhythmic
  - less synchronous

- Later phase = “Mild clonic”
  - more synchronous (nearly clonic)
  - less intense clonic

“Post-ictal ”

- motionless
- ± oral automatism

- EEG:
  - slow waves
  - bil. diffuse / continuous

- all 6 phases; 19/26 seizures
  - Patient 1 : 4 out of 6 seizures
  - Patient 2 : all 6 seizures
  - Patient 3 : 9 out of 14 seizures

- some phases can be:
  - shorter or lacking
  - longer or more pronounced

“diversity of seizure manifestations” in literature

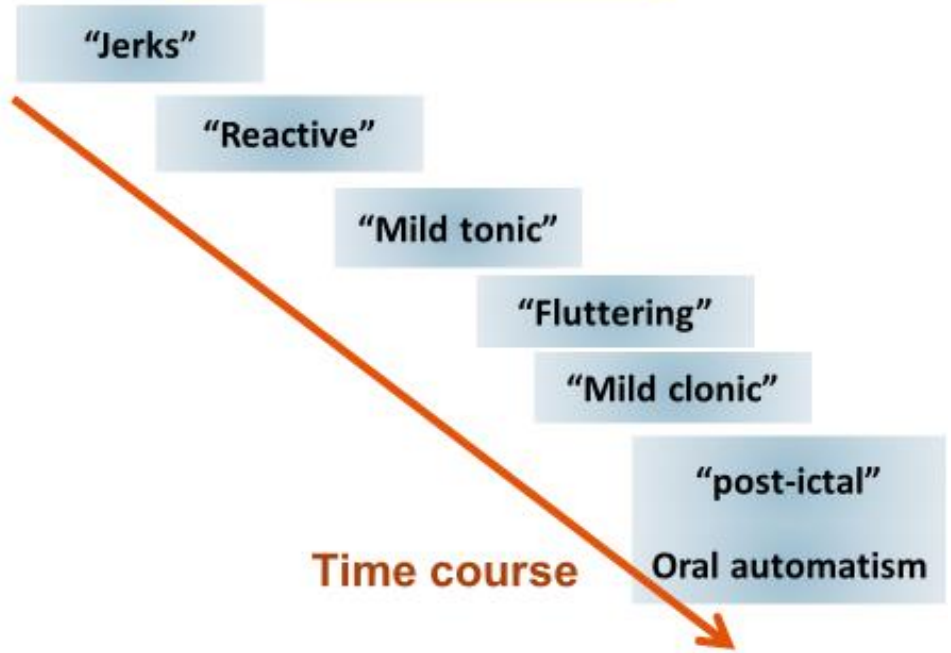
- focal-onset seizures
- secondary generalization
- originate from either side

Hyperexcitability of the brain

widespread and **unstable**

→ the seizures **easily propagate**

Seizure sequence



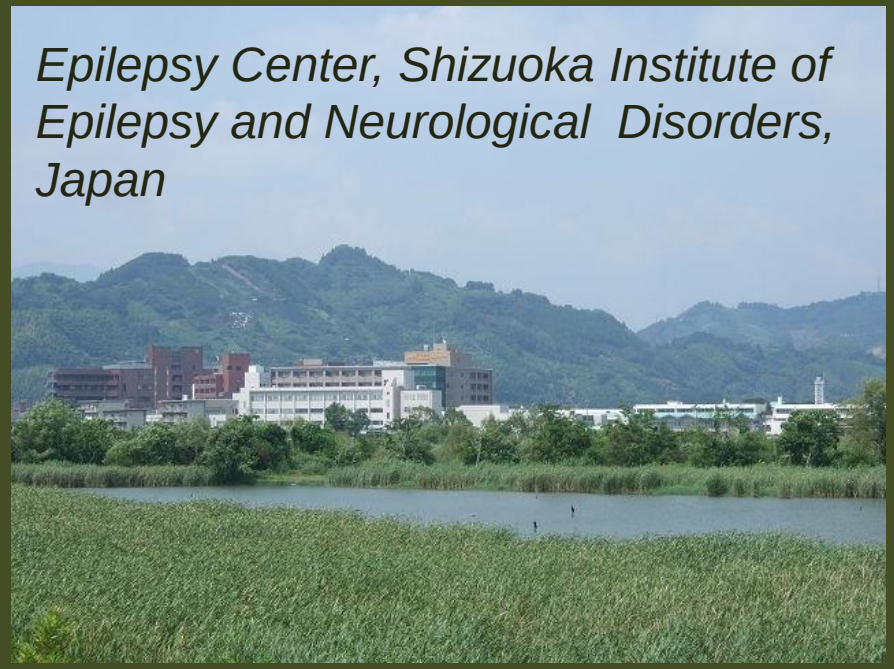
Cluster (monthly-yearly)
during sleep

Onset < early childhood
Fever sensitivity
Intellectual disability
/Autism

These characteristic features may allow us to suspect PCDH19 disorder.

Note; significant phenotypic variability in epilepsy has been recognized

Pediatric neurologists



child-care specialists

Psychiatrists, Neurologists

pediatric clinical psychologists

Laboratory / EEG technicians

Neurosurgeons

Thank you