epiXchange

Epigenetic diagnostic biomarkers in FCDs

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DESIRE
Development & Epilepsy

Strategies for Innovative Research to
Improve Diagnosis, Prevention and Treatment
In Children with Difficult to Treat Epilepsy

Focal Cortical Dysplasia

- Malformation of cortical development
- Very severe form of epilepsy in children
- Pathogenesis unclear (subtype-specific?)
- MRI imaging fails to show abnormalities in some type, difficult to diagnose
- Surgery will often remove large sections of the brain
- Need for molecular biomarkers and new drug targets

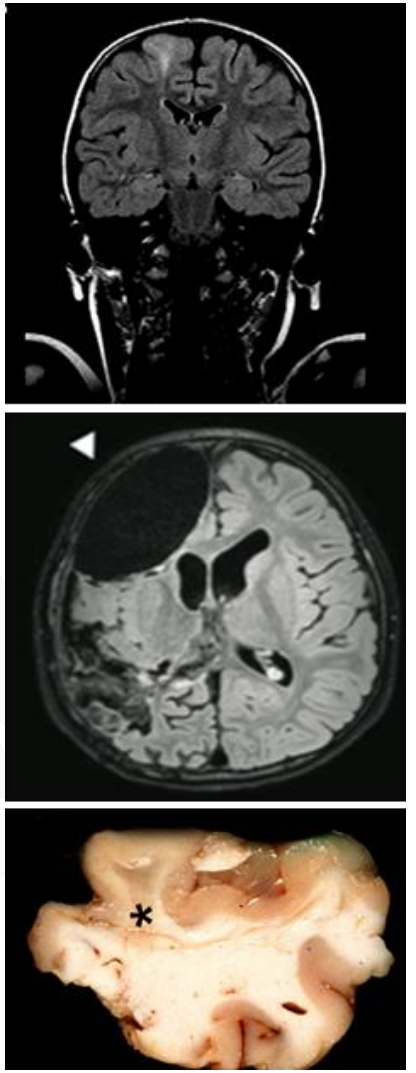


Table 1. The three-tiered ILAE classification system of focal cortical dysplasia (FCD) distinguishes isolated forms (FCD Types I and II) from those associated with another principal lesion (FCD Type III).

FCD Type I (isolated)	Focal cortical dysplasia with abnormal radial cortical lamination (FCD Type Ia) 1a	Focal cortical dysplasia with abnormal tangential cortical lamination (FCD Type Ib) 1b	Focal cortical dysplasia with abnormal radial and tangential cortical lamination (FCD Type Ic) 1c	
FCD Type II (isolated)	Focal cortical dysplasia with dysmorphic neurons (FCD Type IIa) 2a		Focal cortical dysplasia with dysmorphic neurons and balloon cells (FCD Type IIb) 2b	
FCD Type III (associated with principal lesion)	Cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis (FCD Type IIIa) 3a	Cortical lamination abnormalities adjacent to a glial or glioneuronal tumor (FCD Type IIIb) 3b	Cortical lamination abnormalities adjacent to vascular malformation (FCD Type IIIc) 3c	Cortical lamination abnormalities adjacent to any other lesion acquired during early life, e.g., trauma, ischemic injury, encephalitis (FCD Type IIId) 3d

FCD Type III (not otherwise specified, NOS): if clinically/radiologically suspected principal lesion is not available for microscopic inspection.
Please note that the rare association between FCD Types IIa and IIb with hippocampal sclerosis, tumors, or vascular malformations should not be classified as FCD Type III variant.

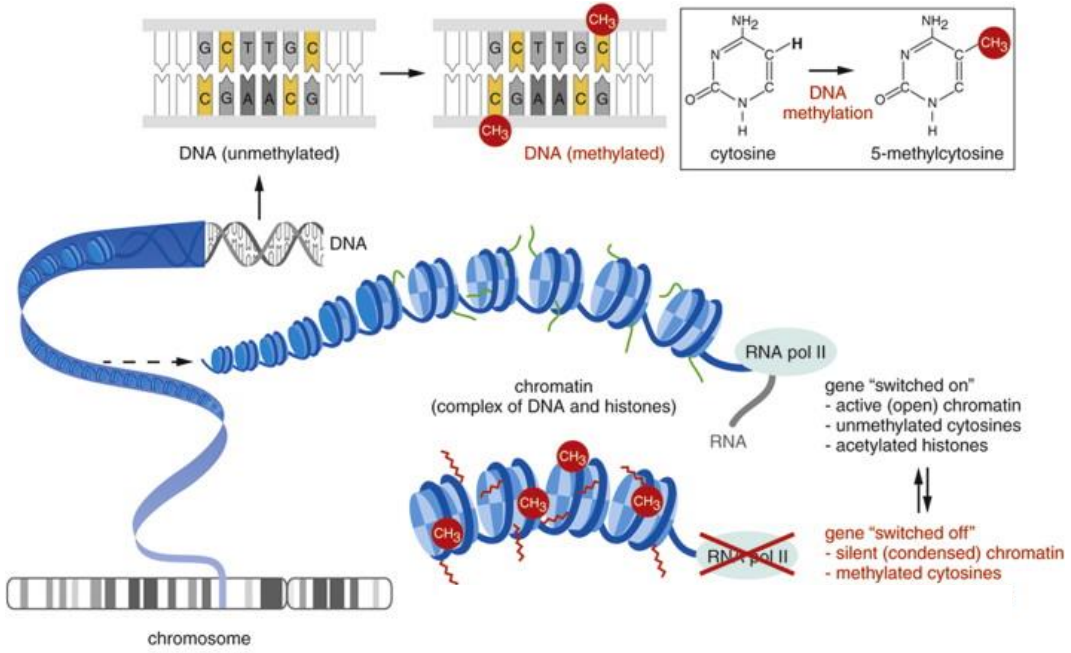
Epigenetics – the unseen operator of the genome

- molecular memory of the cell

"DNA methylation may provide a lifetime record of environmental exposures and a useful source of biomarkers … that may be used in the decision-making process for disease diagnosis, prognosis and treatment." *Nature Reviews Genetics* **13**, 679–692

- reversible! > new treatments?

DNA methylation



Histone modifications

Non-coding RNAs

Bottlenecks

- **Versatility of epigenetic marks** (changes over time, reversible)
- **Complexity** of the epigenetic regulatory system
- **Sample size** (multi-center studies, seq costs, data storage, ethics)
- Cell type specific epigenetic profiles required (**cell atlas**)?
- **Data processing and statistical analysis**, modelling and prediction (machine learning)
- **Technical limitations** at participating sites/clinics,

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