EBM Webinars

Focal epilepsy caused by cortical malformations

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nothing to disclose

FRIEDRICH-ALEXANDER UNIVERSITY ERLANGEN-NÜRNBERG

MEDICAL FACULTY

Universitätsklinikum Erlangen

Today's roadmap

Focal epilepsy caused by cortical malformations

- What is „focal epilepsy" and how to diagnose a seizure
- The European Epilepsy Brain Bank experience with >10.000 patients
- Histopathology is the „gold standard" in medical diagnosis
- Genotype-phenotype correlations pave the way towards precision medicine

EBM Webinars

Focal epilepsy caused by cortical malformations

Epilepsy affects approx. 50 Mio. people worldwide (WHO fact sheet)

Approximately one third of people with epilepsy can be classified as drug-resistant and this proportion is much higher for people with focal epilepsy (Kwan and Brodie 2000).

The estimated prevalence of focal, drug-resistant epilepsy is approx. 30 in 100,000 people (adults and children).

Lopez-Rivera et al. 2022, Epilepsy and Behavior Reports

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What is focal epilepsy and how do diagnose a seizure

Georg is a 22 year old male with a disease onset at age 10 years.

He has 1-2 seizures per day, usually occuring at night.

Over the past 12 years he took various antiseizure medications (in sufficient dosage).

courtesy of the ILAE Academy and Dr. Irina Oane, Bucharest, Romania

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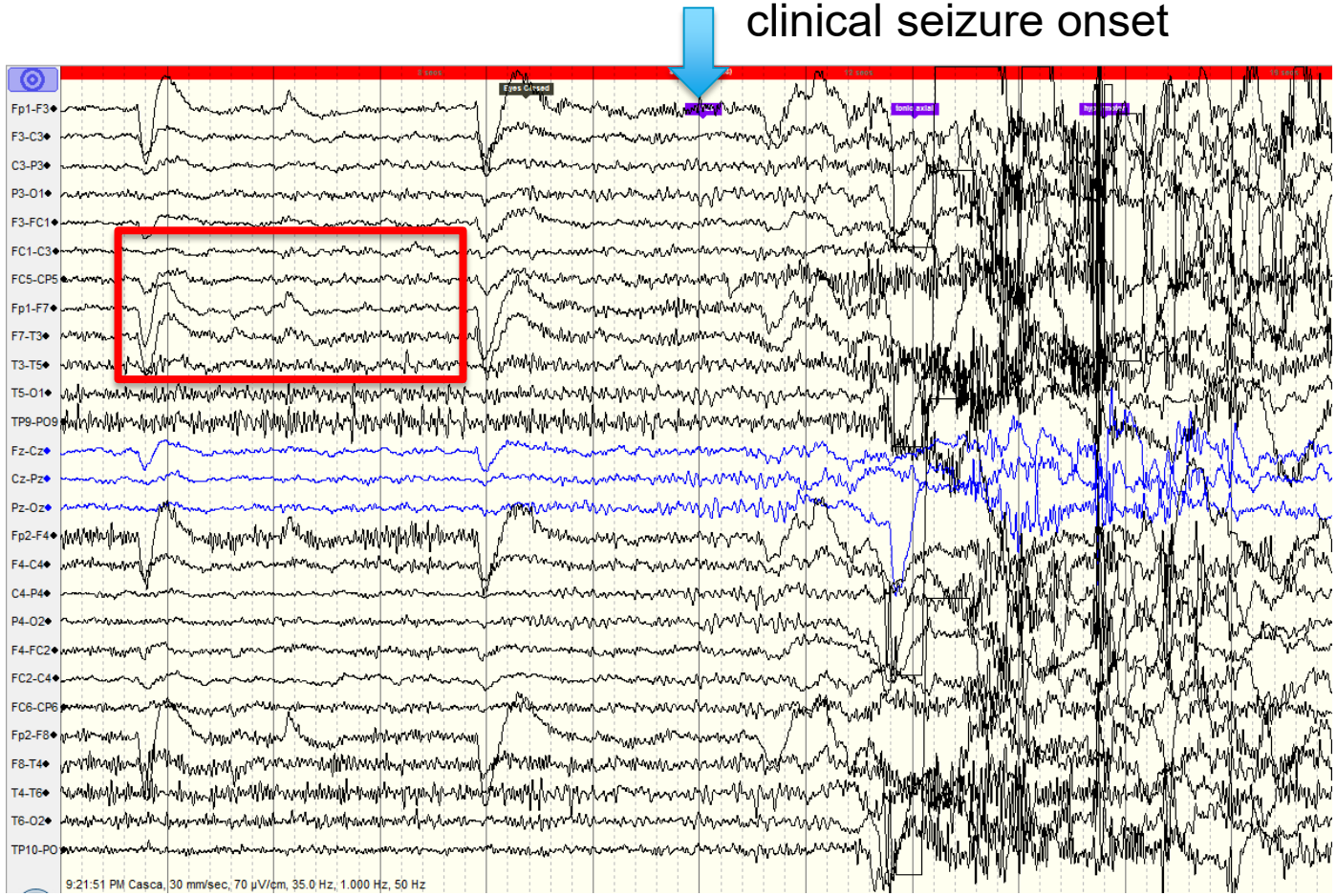
What is focal epilepsy and how do diagnose a seizure



low amplitude rhythmic teta discharge left frontal-temporal

courtesy of the ILAE Academy and Dr. Irina Oane, Bucharest, Romania

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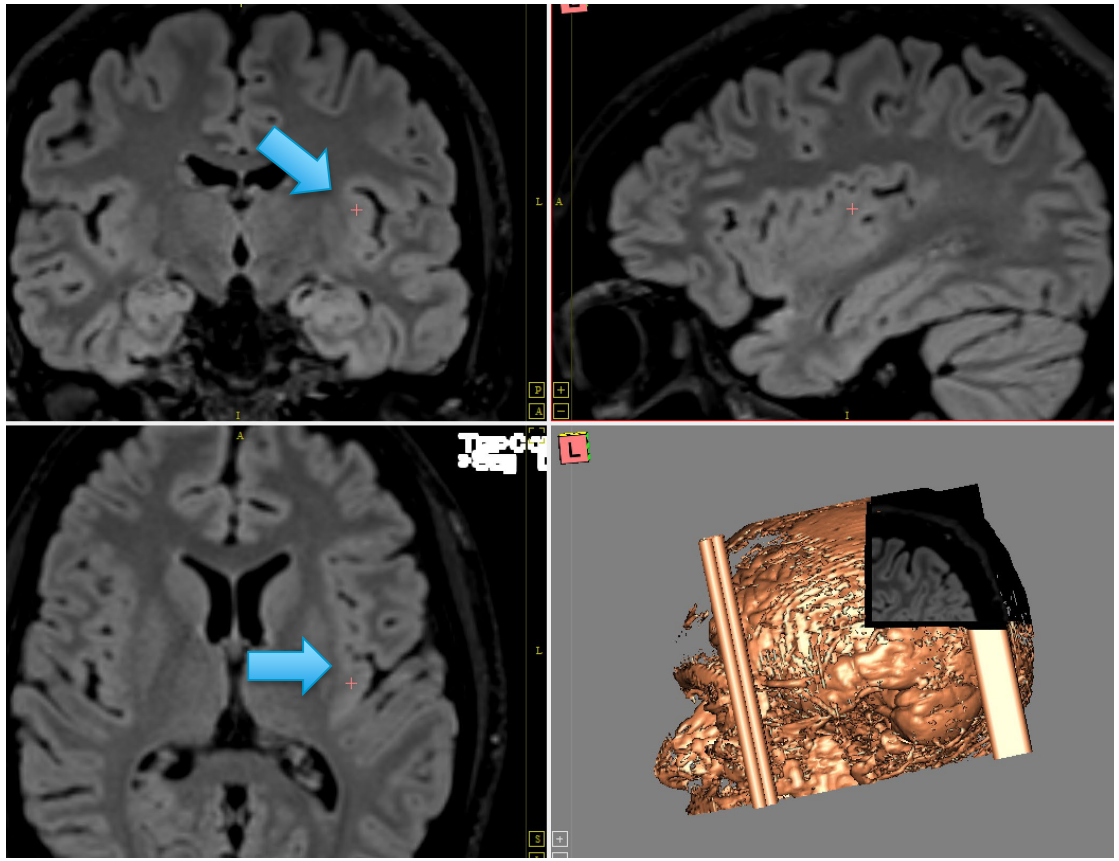
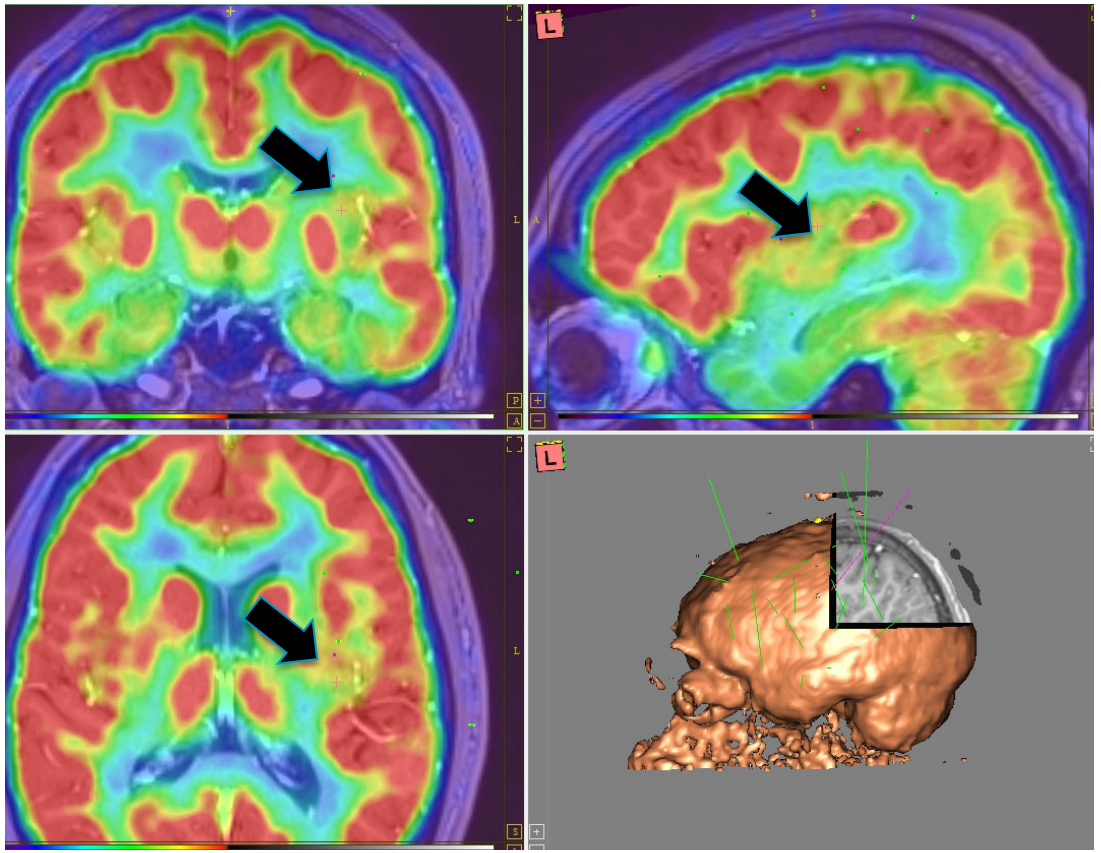
What is focal epilepsy and how do diagnose a seizure





courtesy of the ILAE Academy and Dr. Irina Oane, Bucharest, Romania

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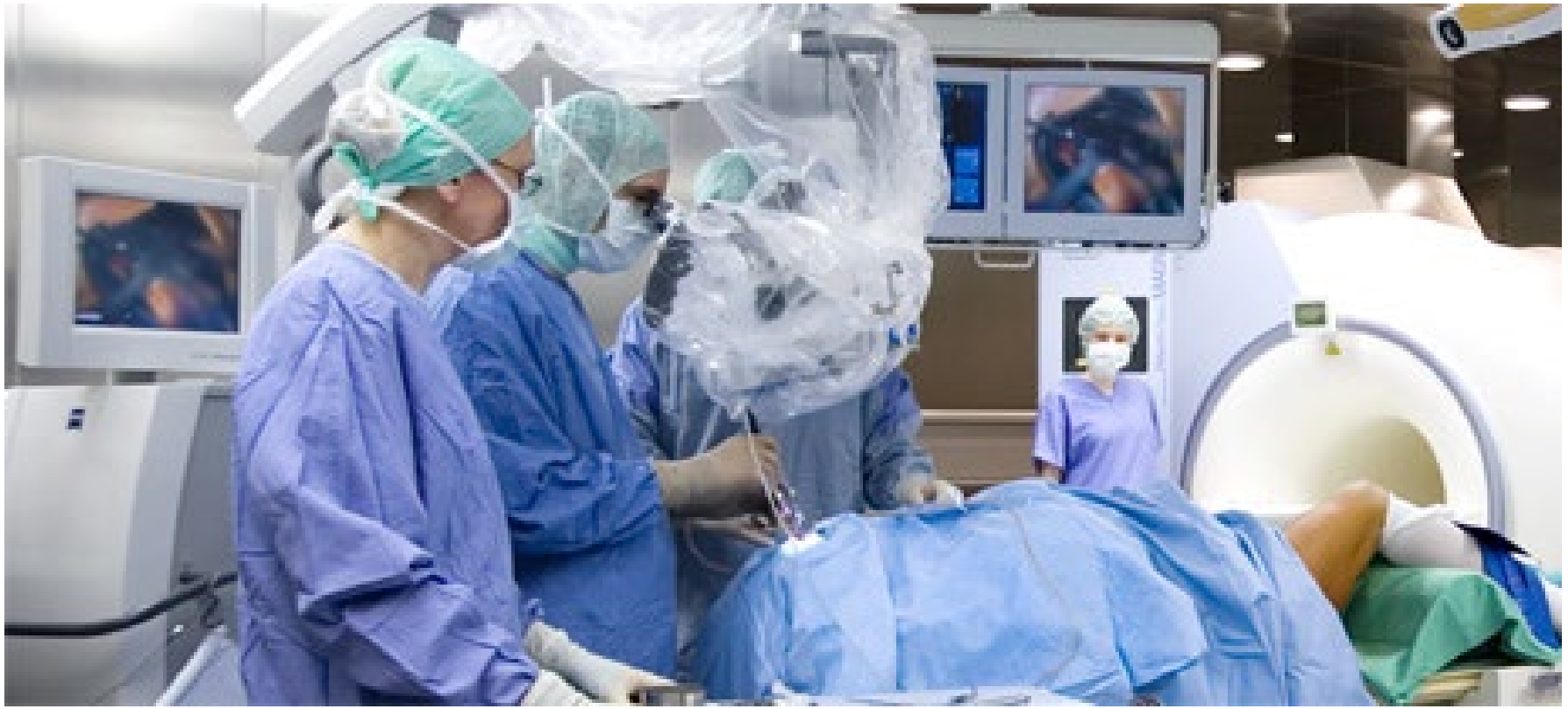
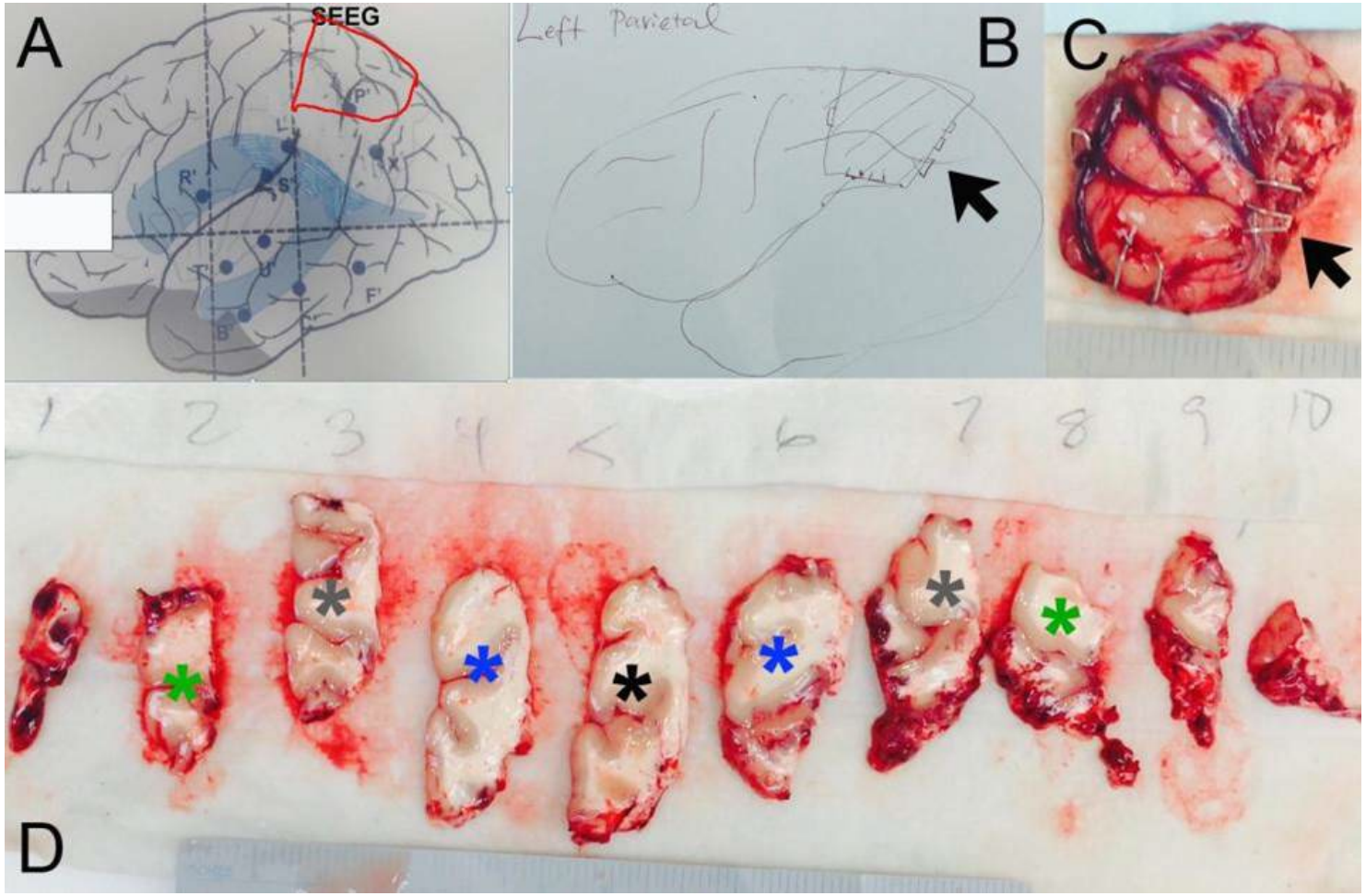
Modern epilepsy surgery in a „Brain Suite“



Surgical Pathology of cortical malformations



Clinico-anatomical and molecular correlations (genotype-phenotype) in human epilepsy surgery brain tissue

Blümcke et al. Epilepsia. 2016 Mar;57(3):348-58

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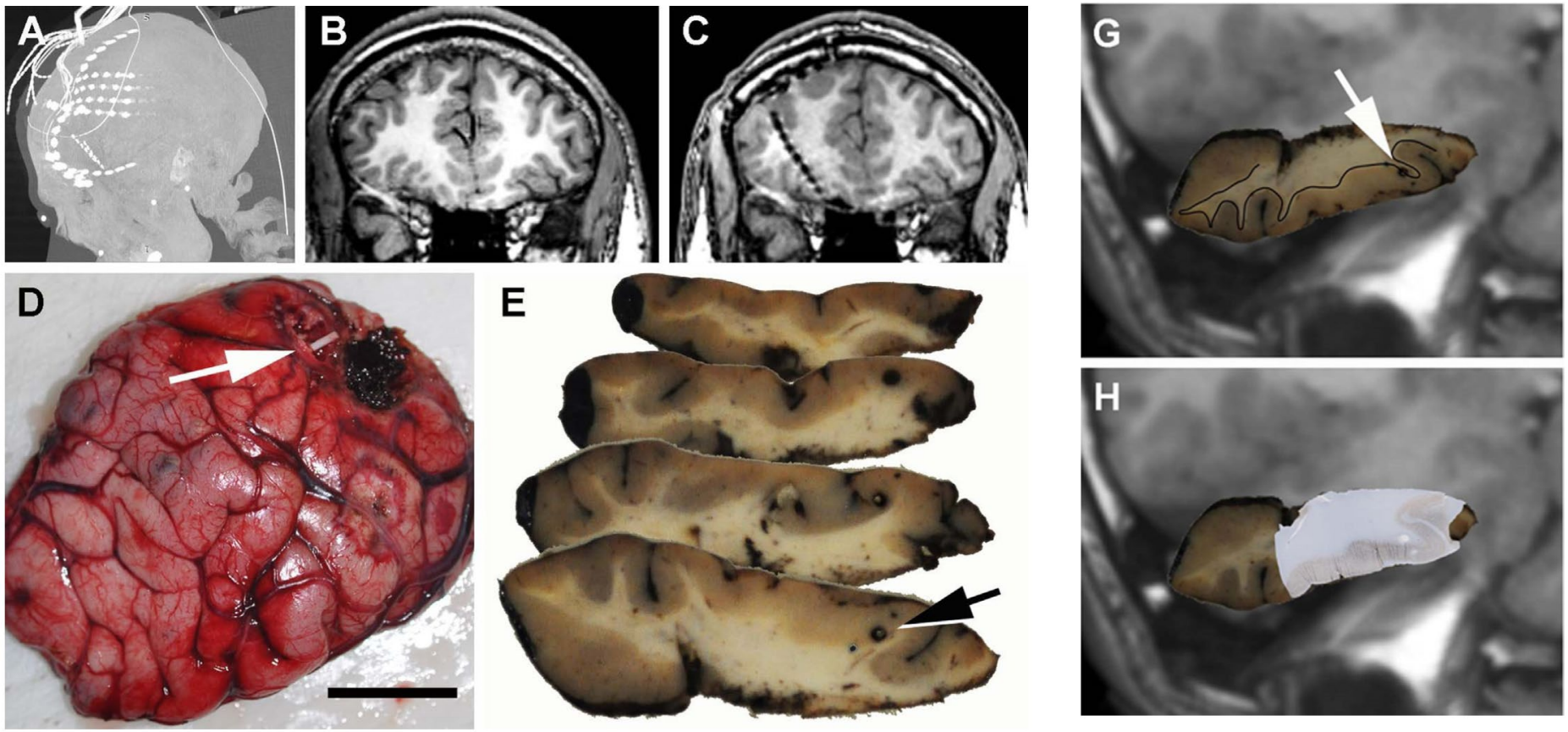
Coregistration studies in epilepsy surgery



Rampp et al. Clin. Neurophysiol. 132 (2021):782-792

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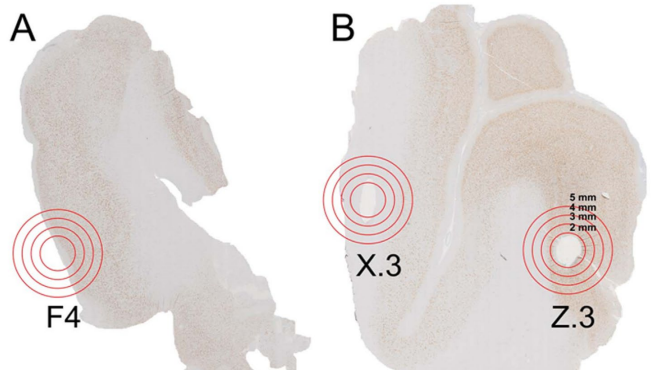
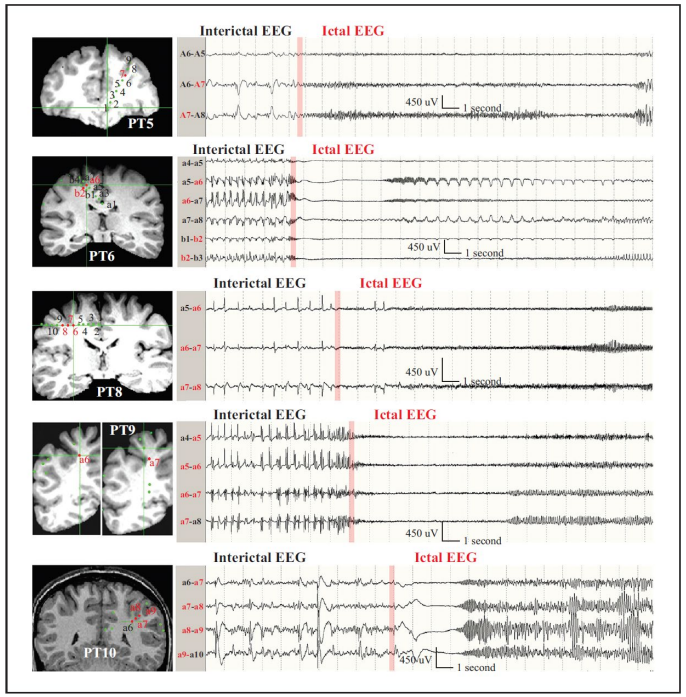
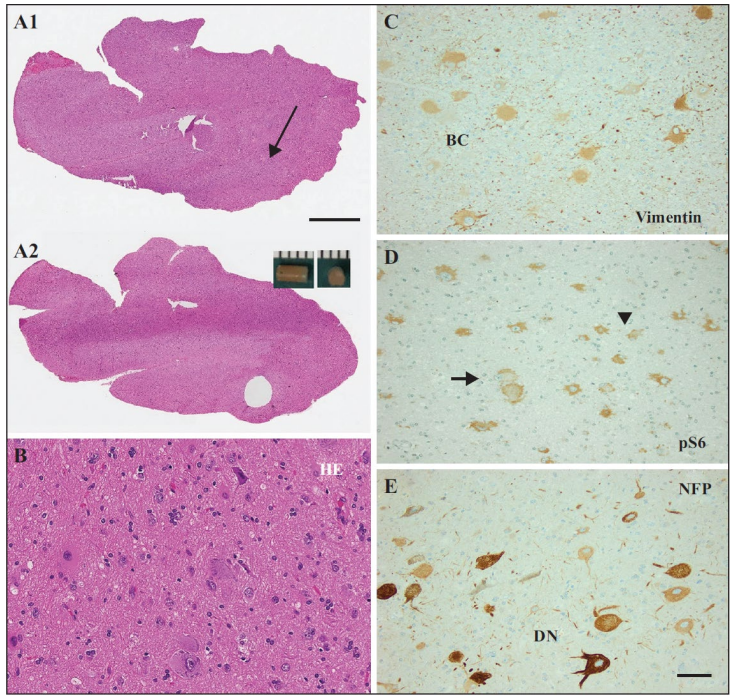
Coregistration studies in epilepsy surgery



Rampp et al. Clin. Neurophysiol. 132 (2021):782-792

NSx – EPI – NP - Genetics





Ying et al. Epileptic Dis. 21 (2019):65-77

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- **The European Epilepsy Brain Bank experience with >10.000 patients**
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- Genotype-phenotype correlations pave the way towards precision medicine

The NEW ENGLAND JOURNAL of MEDICINE

EpiCARE

ORIGINAL ARTICLE

Histopathological Findings in Brain Tissue Obtained during Epilepsy Surgery

I. Blumcke, R. Spreafico, G. Haaker, R. Coras, K. Kobow, C.G. Bien, M. Pfäfflin, C. Elger, G. Widman, J. Schramm, A. Becker, K.P. Braun, F. Leijten, J.C. Baayen, E. Aronica, F. Chassoux, H. Hamer, H. Stefan, K. Rössler, M. Thom, M.C. Walker, S.M. Sisodiya, J.S. Duncan, A.W. McEvoy, T. Pieper, H. Holthausen, M. Kudernatsch, H.J. Meencke, P. Kahane, A. Schulze-Bonhage, J. Zentner, D.H. Heiland, H. Urbach, B.J. Steinhoff, T. Bast, L. Tassi, G. Lo Russo, C. Özkara, B. Oz, P. Krsek, S. Vogelgesang, U. Runge, H. Lerche, Y. Weber, M. Honavar, J. Pimentel, A. Arzimanoglou, A. Ulate-Campos, S. Noachtar, E. Hartl, O. Schijns, R. Guerrini, C. Barba, T.S. Jacques, J.H. Cross, M. Feucht, A. Mühlebner, T. Grunwald, E. Trinka, P.A. Winkler, A. Gil-Nagel, R. Toledano Delgado, T. Mayer, M. Lutz, B. Zountsas, K. Garganis, F. Rosenow, A. Hermsen, T.J. von Oertzen, T.L. Diepgen, and G. Avanzini, for the EEBB Consortium*

9523 patients
36 centers
12 EU countries

Minimal Data Set
Histopath Diagnosis
Sex
Side & Location

Age @ onset
Disease duration
Year of surgery

Sz outcome @ 12m
(Engel1A / ILAE 1)

Blumcke et al., NEJM 377:1648-1656, 2017

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European Epilepsy Brain Bank

Top 10 diagnoses in adults vs. Children (MCD entities in red color)

European Reference Network
for rare or low prevalence complex diseases

ADULTS	#	%	ILAE 1	Children	#	%	ILAE 1
HS	3070	44.5%	66.0%	**FCD II**	447	17.0%	70.7%
Ganglioglioma	602	8.7%	72.3%	**HS**	394	15.0%	74.5%
No Lesion	577	8.4%	52.9%	**Ganglioglioma**	384	14.6%	88.4%
FCD II	412	6.0%	66.6%	**DNT**	186	7.1%	78.6%
Cavernoma	404	5.9%	68.9%	**FCD I**	167	6.4%	54.3%
DNT	379	5.5%	66.0%	**No Lesion**	161	6.1%	58.4%
Glial Scar	310	4.5%	42.7%	**Glial Scar**	151	5.8%	65.9%
mMCD	172	2.5%	56.1%	**mMCD**	107	4.1%	49.4%
FCD nos	118	1.7%	56.2%	**Tuber (TSC)**	93	3.5%	59.2%
Oligodendroglioma (mixed)	114	1.7%	64.9%	**FCD nos**	88	3.4%	56.3%
Total	6158	**89.2%**	**58.6%**	**Total**	2178	**83.0%**	**66.4%**

HS – hippocampal sclerosis
FCD – focal cortical dysplasia
DNT – low grade brain tumor
mMCD – mild MCD
MCD – cortical malformation

Blumcke et al., NEJM 377:1648-1656, 2017

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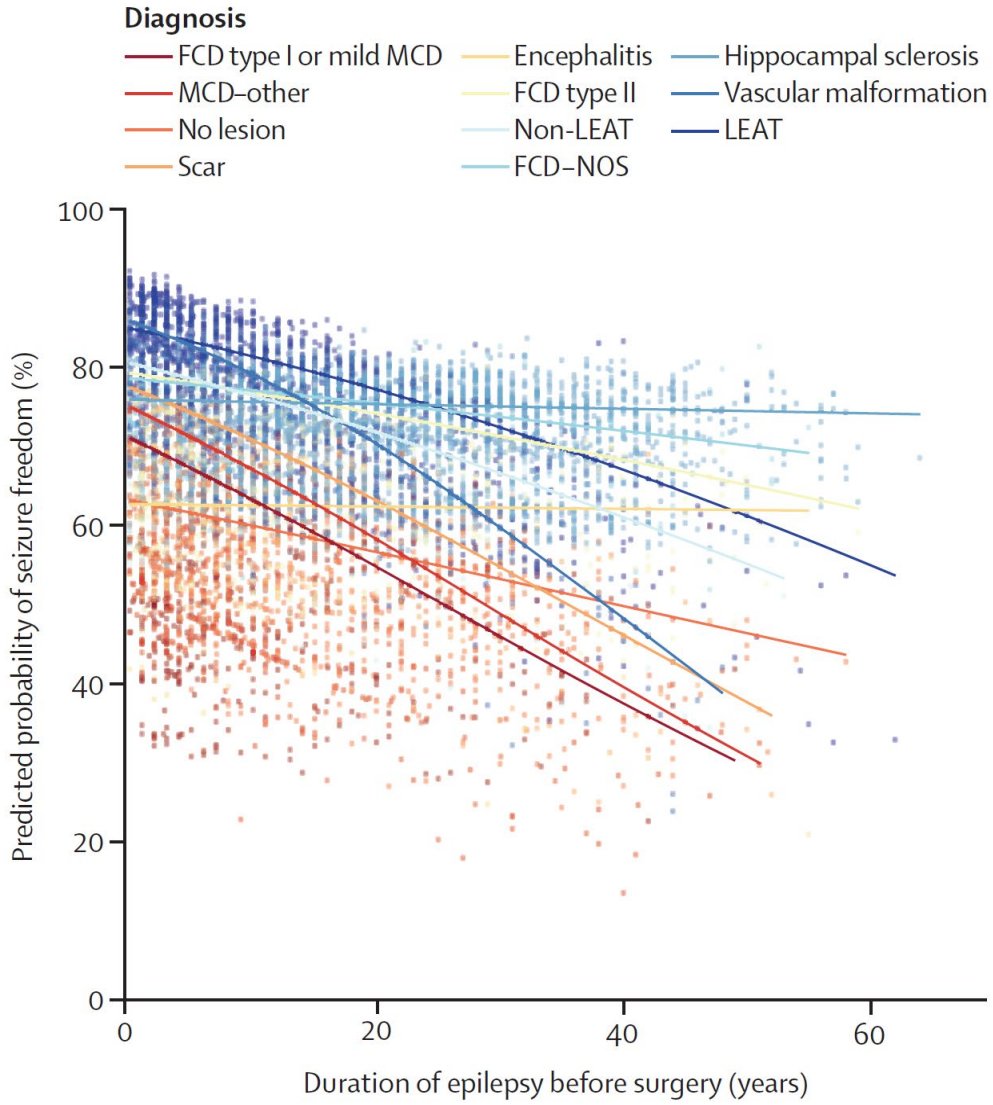
European Epilepsy Brain Bank outcome study



- **A histopathology based prediction model for post-surgical seizure freedom (5 years)**
- **Disease duration and localization of lesion play a major role (probability decreases 1% per year of active seizures)**

Lamberink, Otte, Blumcke and Braun. Lancet Neurol 2020 19(9): 748-757

Jehi et al. Lancet Neurol 2015 14(3): 283-90

Najm, Jehi et al. Epilepsia 2013 54(5): 772-82

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Today's roadmap

EpiCARE

Focal epilepsy caused by cortical malformations

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International consensus classification for Focal Cortical Dysplasia (FCD)

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

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.

Blumcke et al. Epilepsia (2011)

The pre-pandemic „old normal" ...

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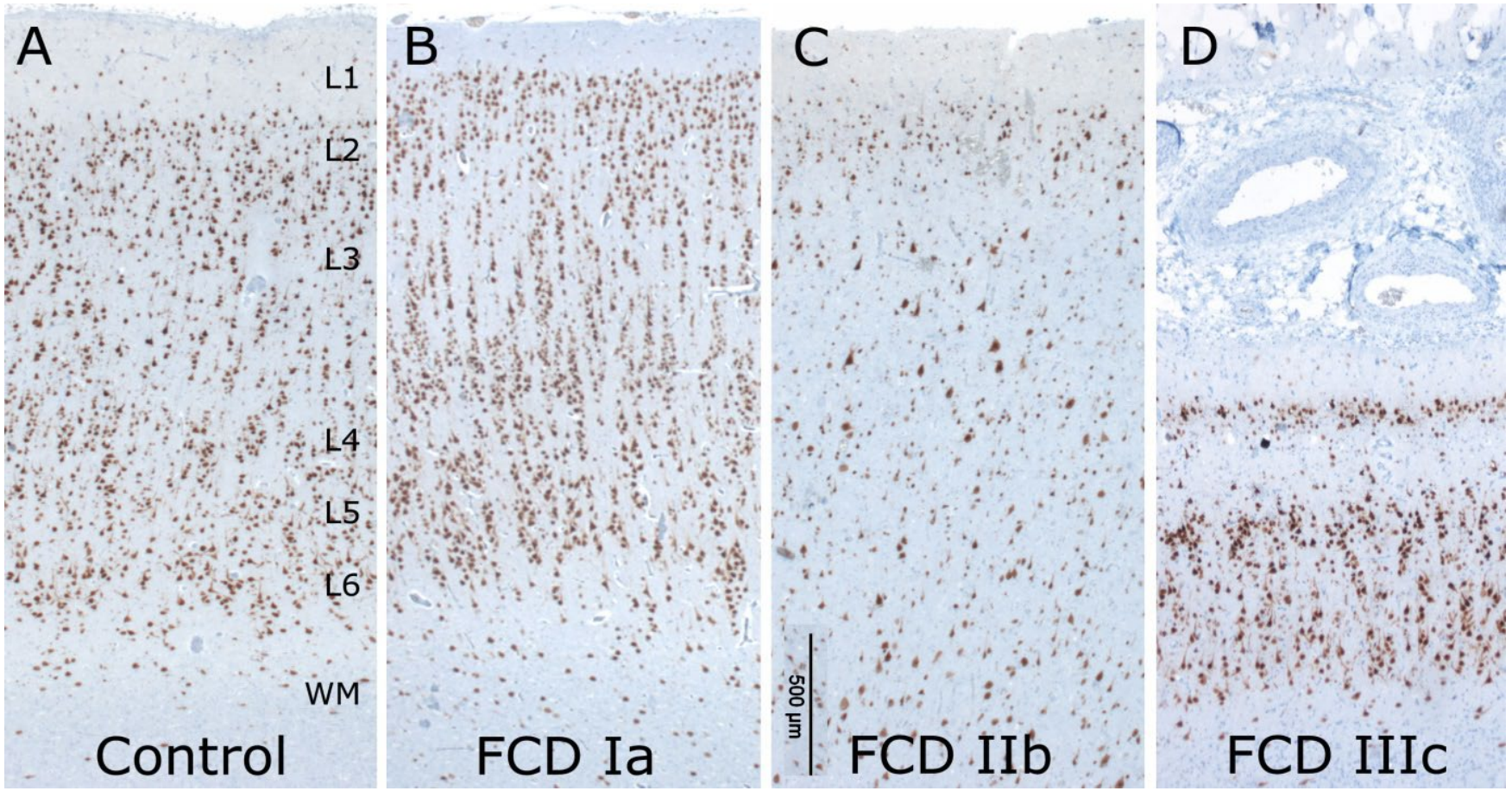
Distinct histopathological signatures define FCD subtypes (NeuN immunohistochemistry)



Blumcke et al. Epilepsia (2011) 52:158-174

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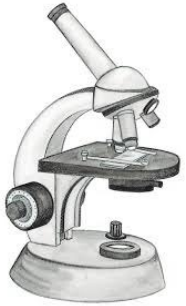

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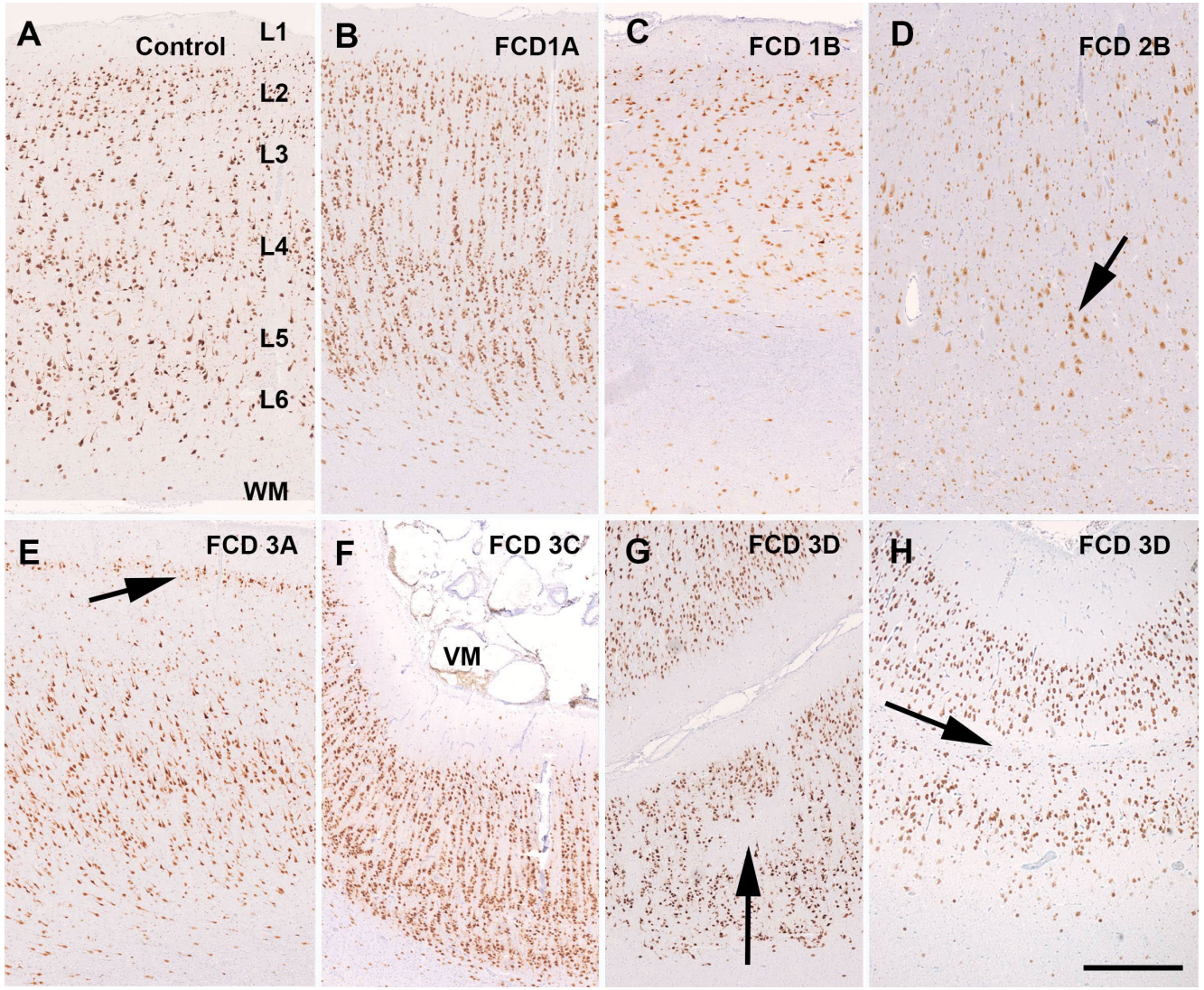
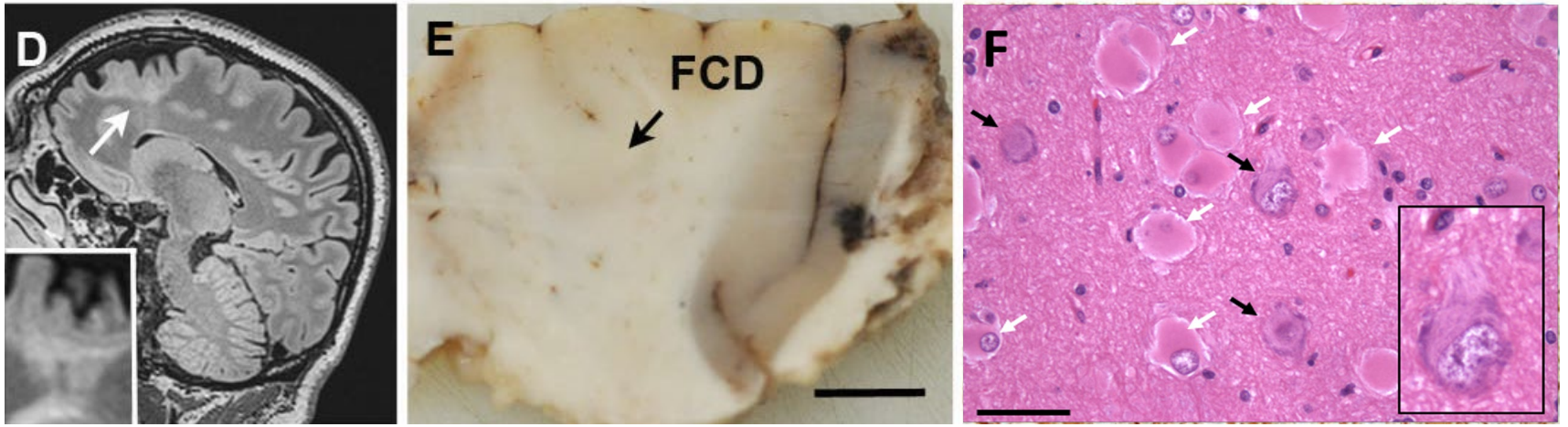


Najm et al. Epilepsia (in revision)

EEBB TOP#3: FCD Type II

Numbers		Female	Left	Frontal	Onset	Duration	ILAE 1
# 859	9.0%	47.4%	46.7%	54%	5.2 y	14 y	65.2%
IIA	31.5%	46.6%	50%	47.8%	5.3 y	11.5 y	55.8%
IIB	69.5%	45.3%	49%	54.4%	5.3 y	13.5 y	72.7%



Blumcke et al., NEJM 377:1648-1656, 2017

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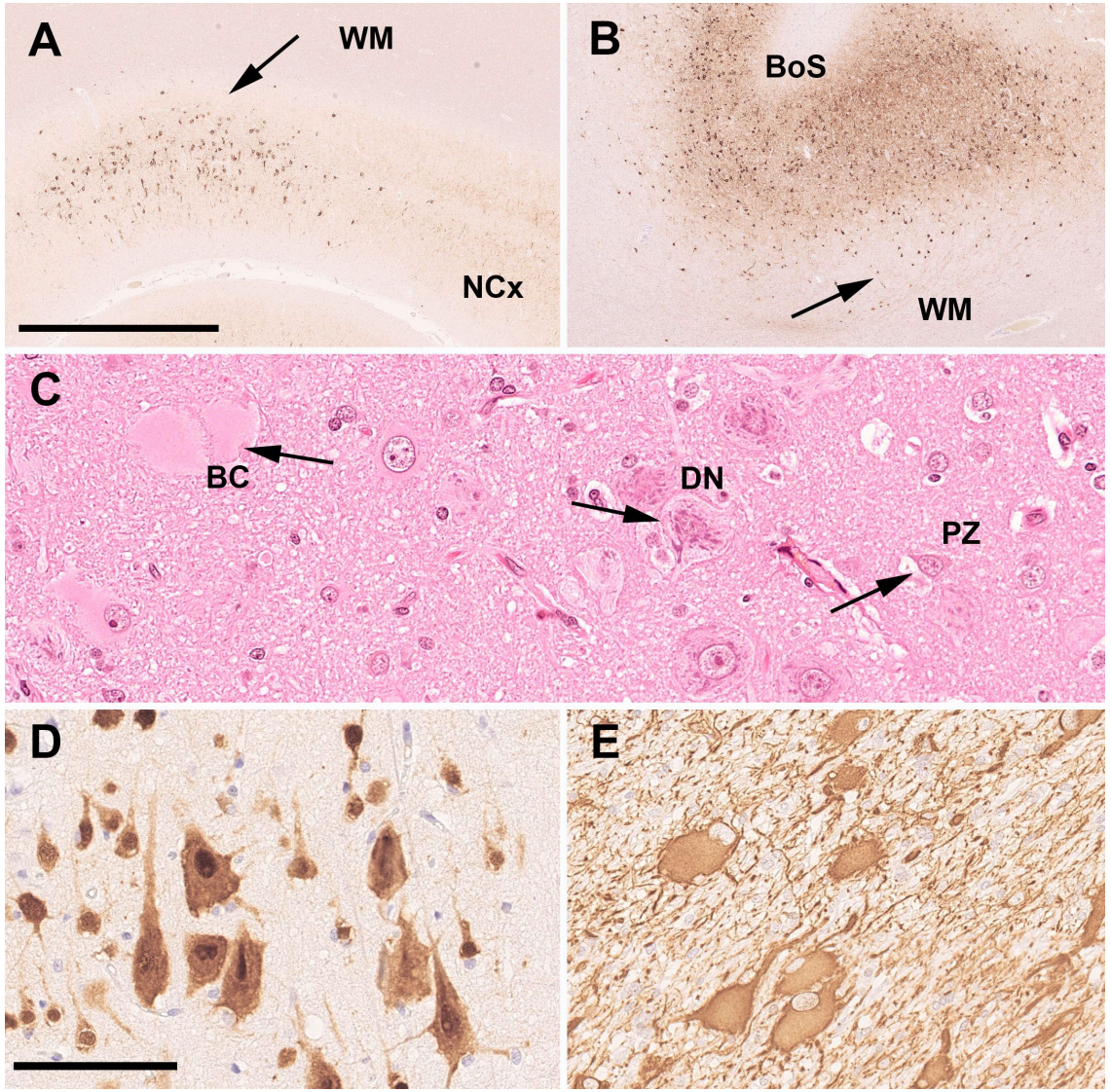
EEBB TOP#3: FCD Type II



→ you want to see live microscopy ?

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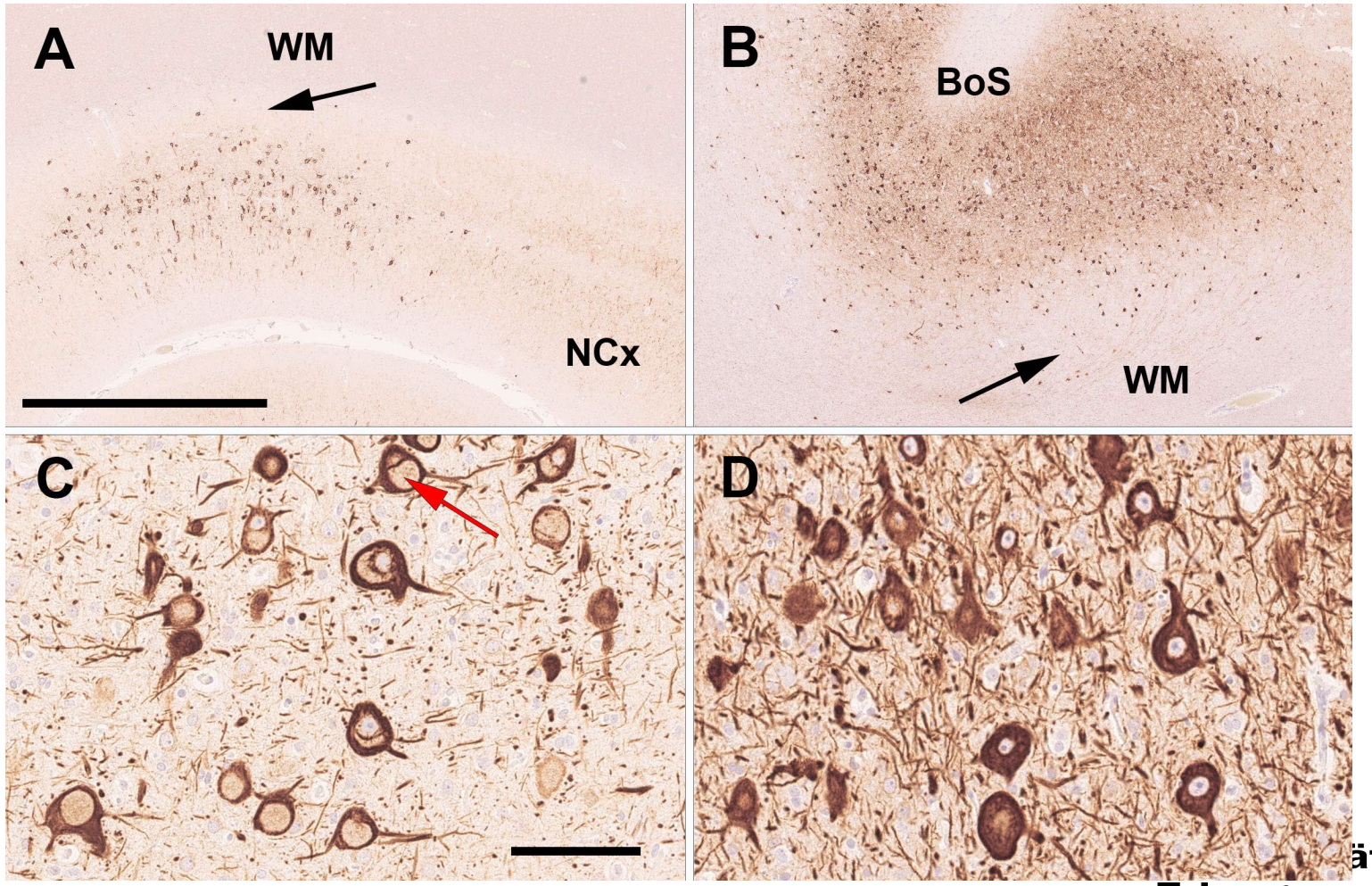
EEBB TOP#3: FCD Type II

FCD IIA
with
DEPDC5
mutation

cause an
autophagosome-
altered
phenotype



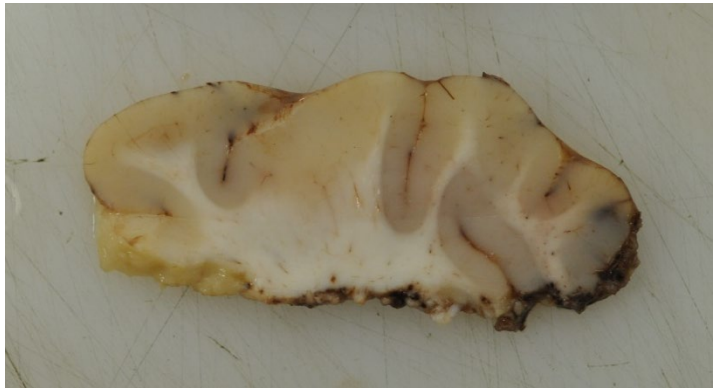
FCD IIB
with
MTOR mutation

cause an
neural
migration-
altered
phenotype

ätsklinikum
Erlangen

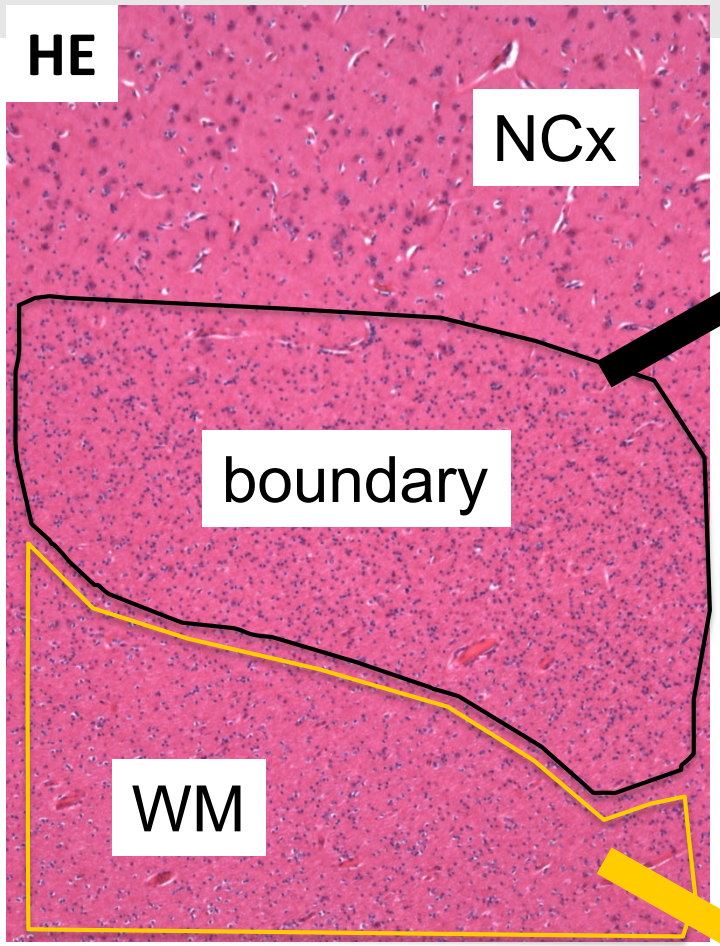
EEBB TOP#4: no lesion

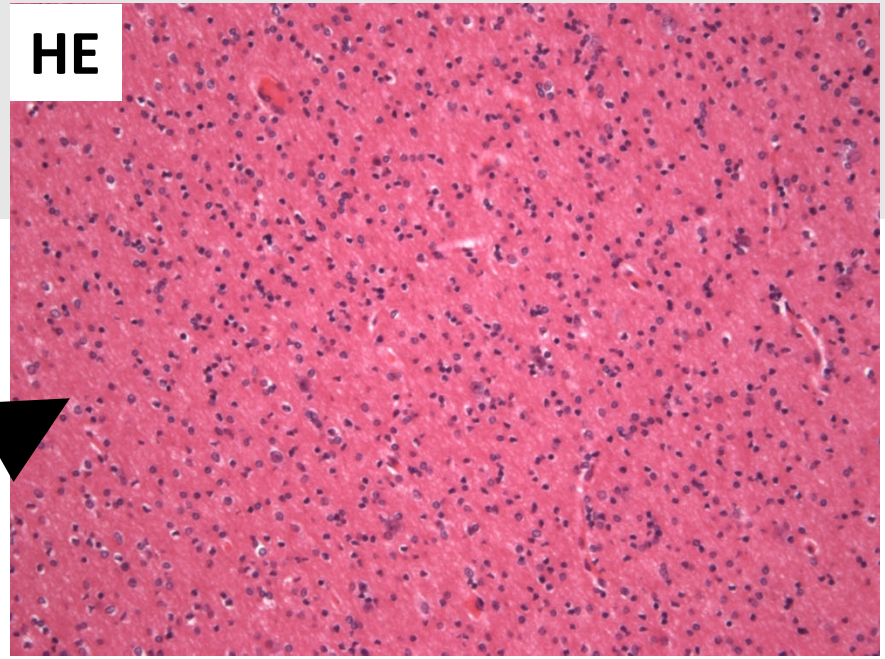
	Numbers		Onset	Duration	ILAE 1
Adult	# 577	10.4 %	15.4 y	17.9 y	48.7 %
Children	# 161	14.6 %	4.4 y	6.5 y	55.2 %

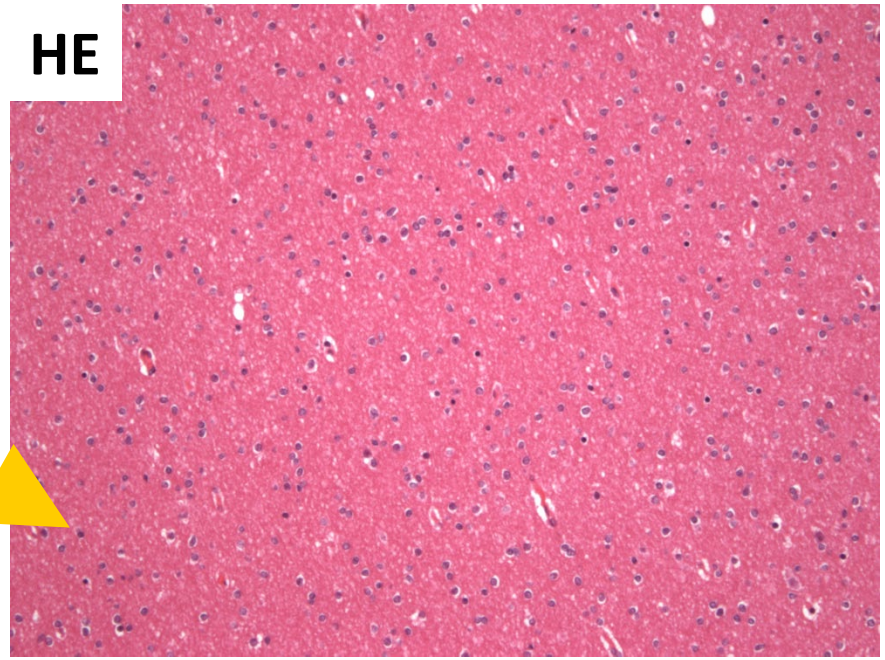


Blumcke et al., NEJM 377:1648-1656, 2017

Schurr et al., Brain Pathol 27: 26-35, 2017


HE
NCx
boundary
WM


HE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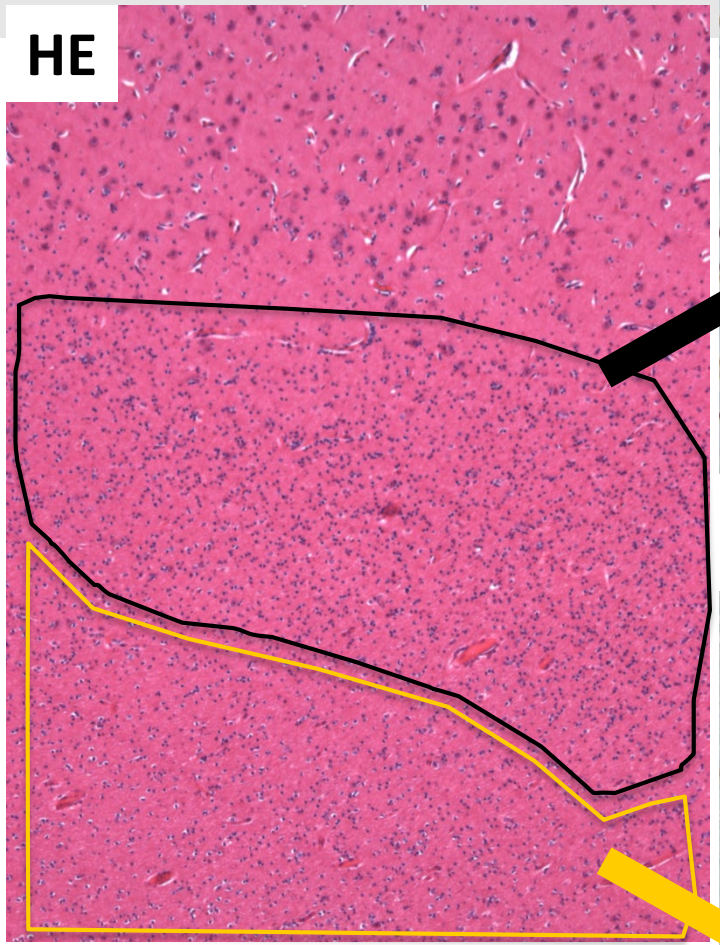
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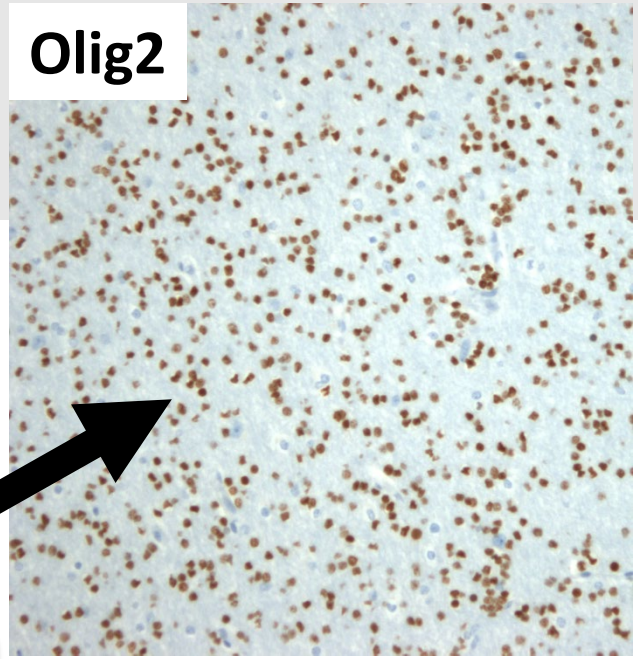
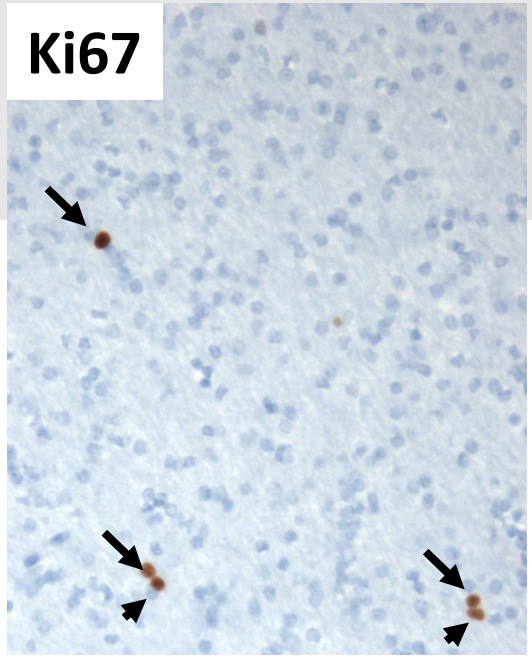
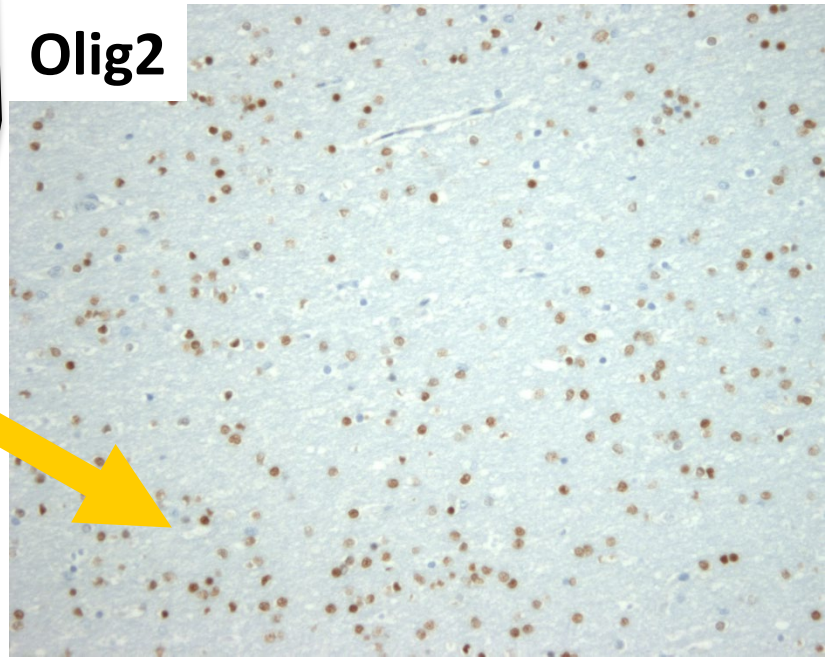
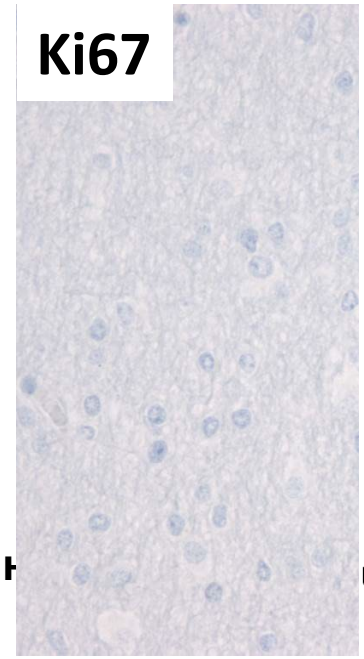
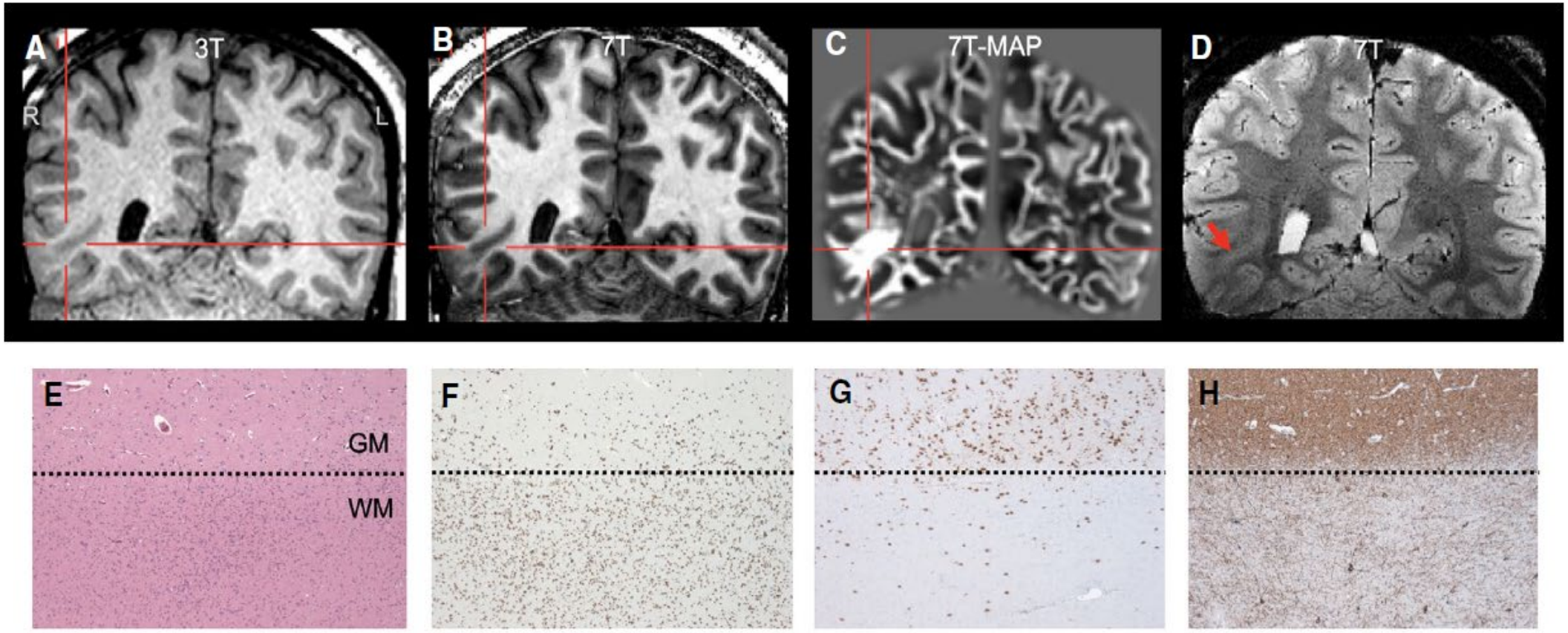

Olig2


Ki67


Olig2


Ki67

MOGHE: mMCD with proliferative oligodendroglial hyperplasia in (frontal lobe) epilepsy



Irene Wang et al. Epilepsia (2020); Lin et al. Clin Neurophysiol (2020)

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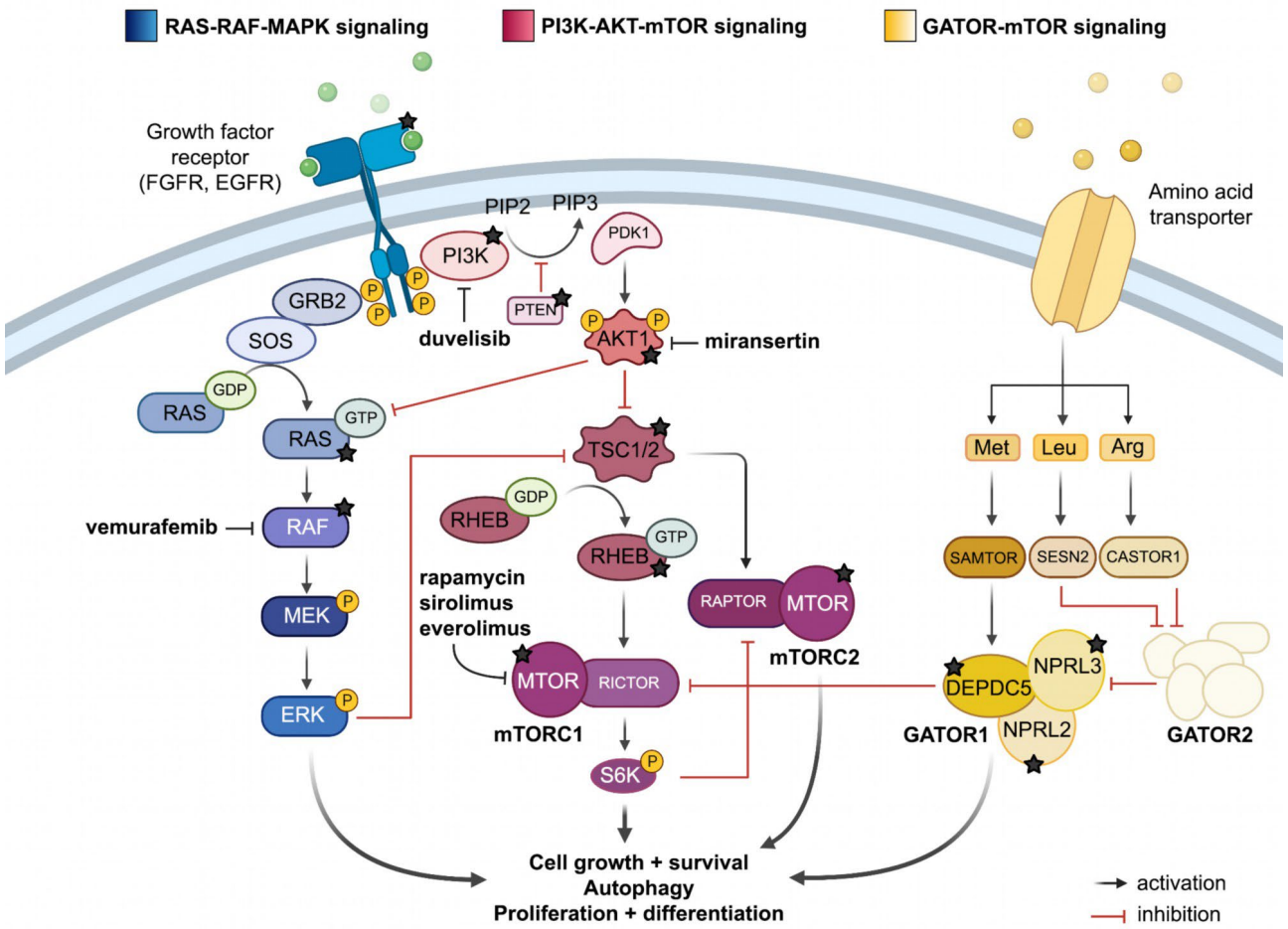
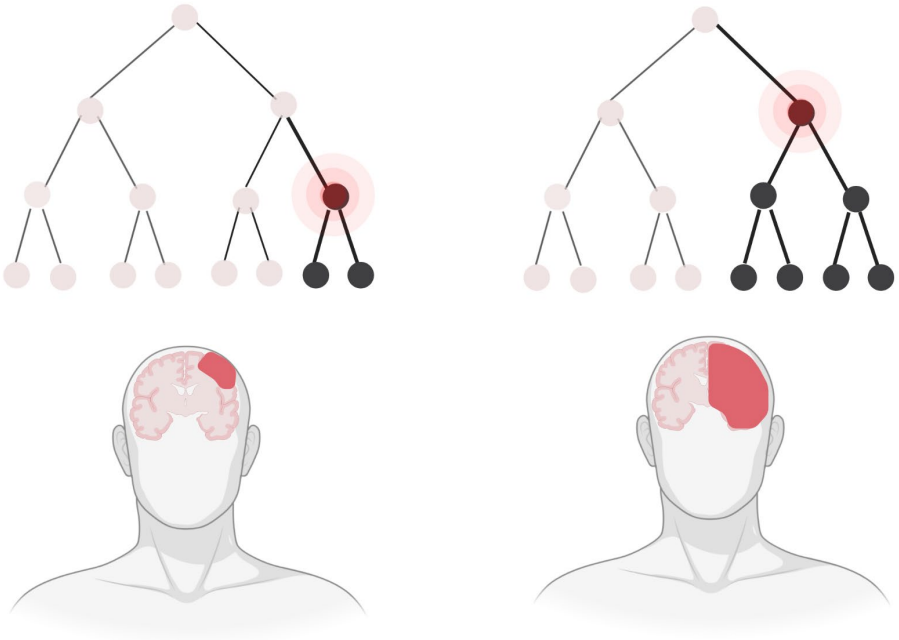
Timing of the acquired genetic lesion determines the size and the gene pathway the histopathological phenotype





Blumcke et al. Lancet Neurol. (2021) 20:943-955

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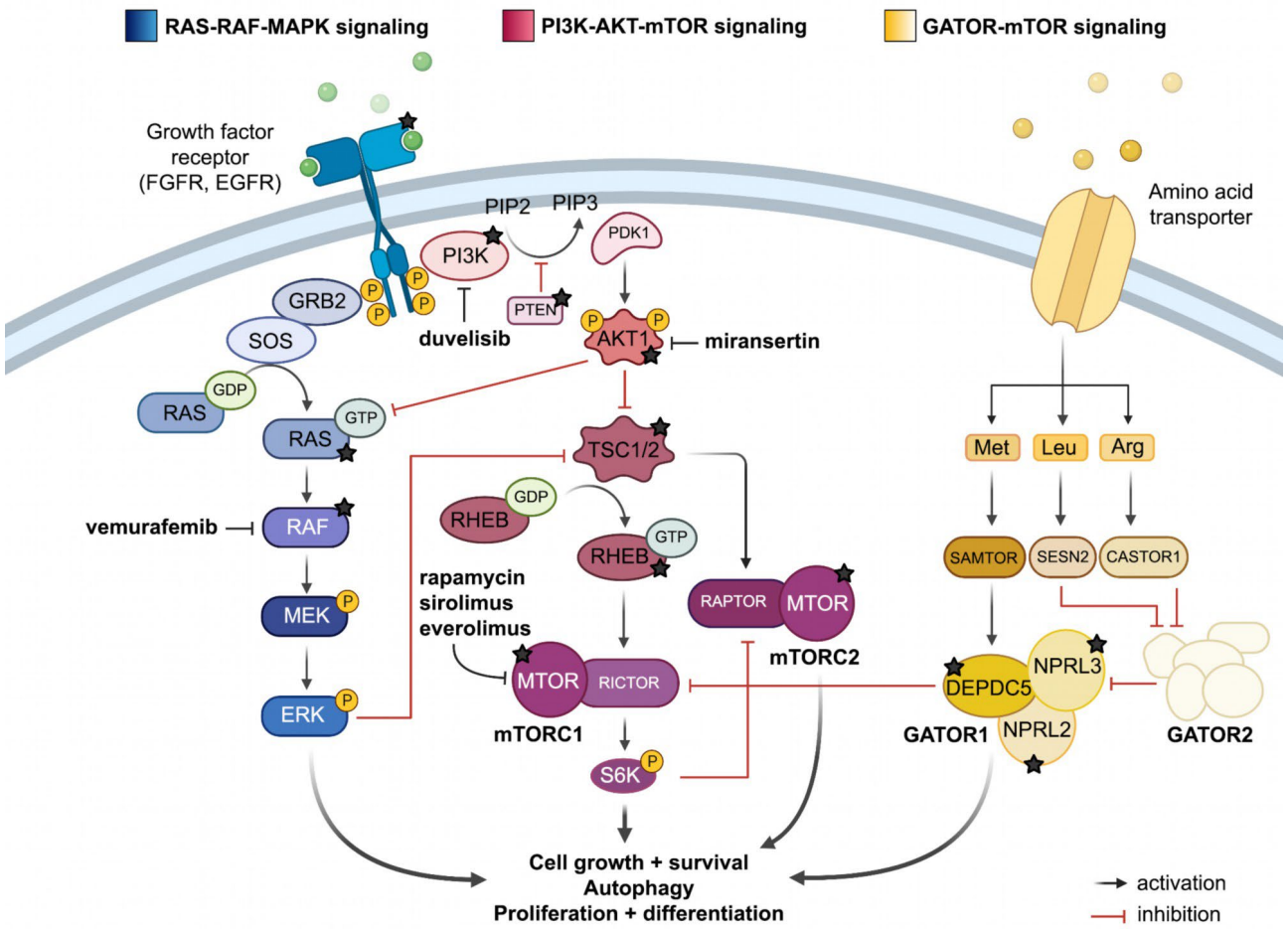

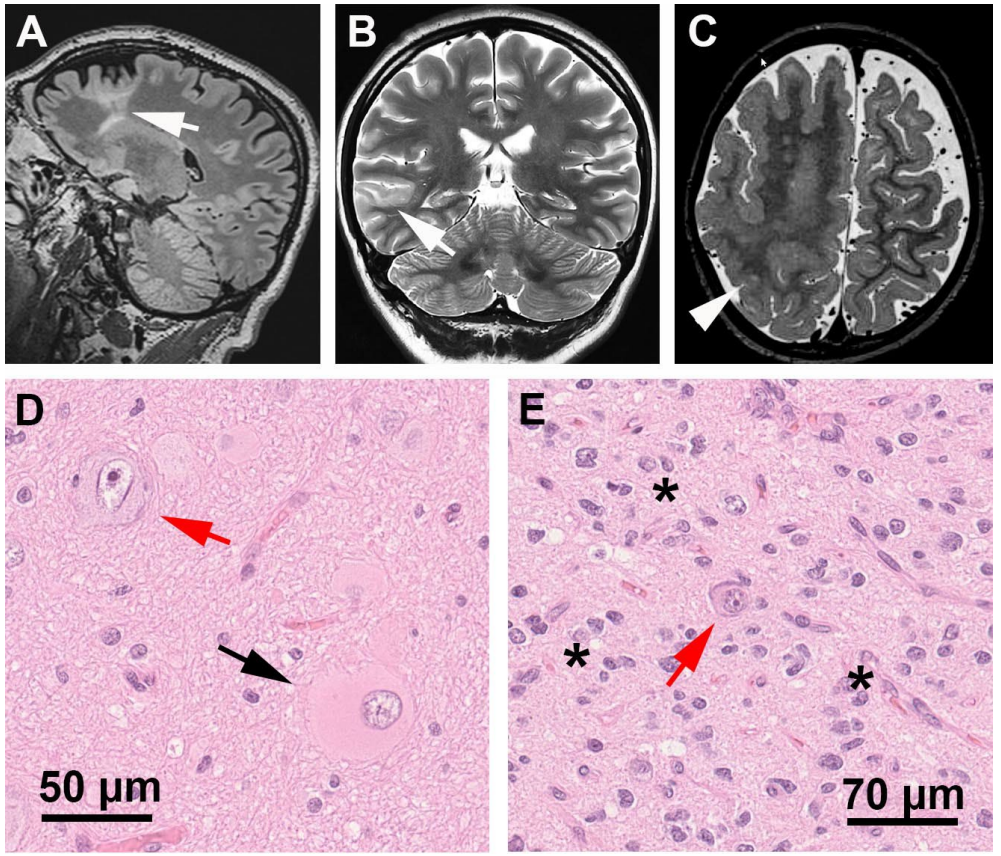

Blumcke et al. Lancet Neurol. (2021) 20:943-955

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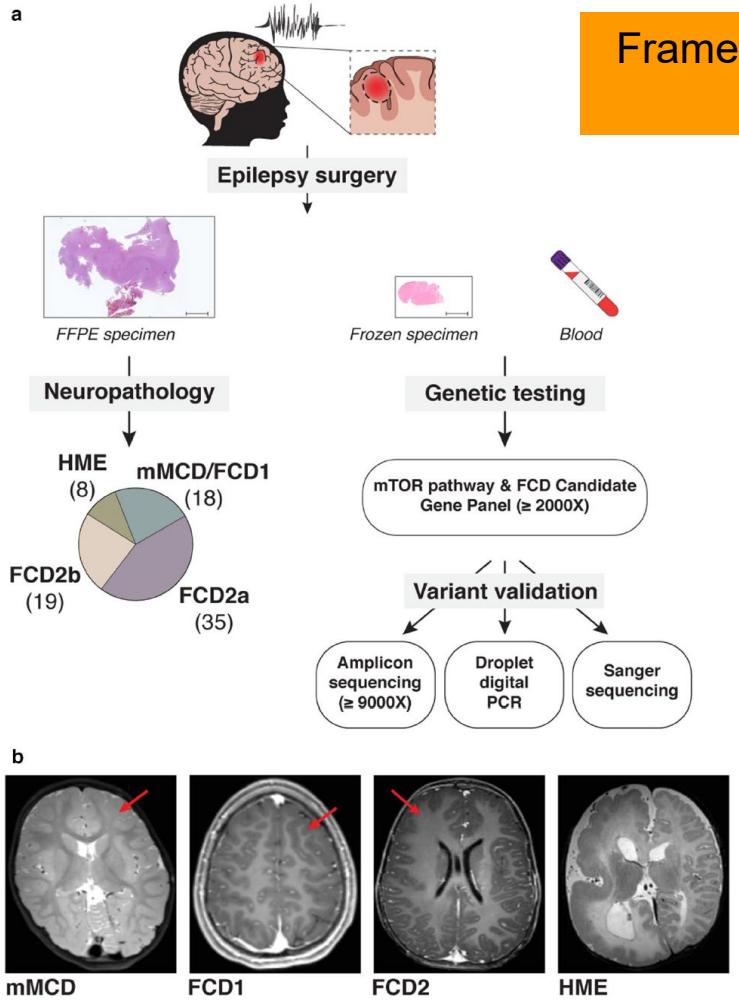
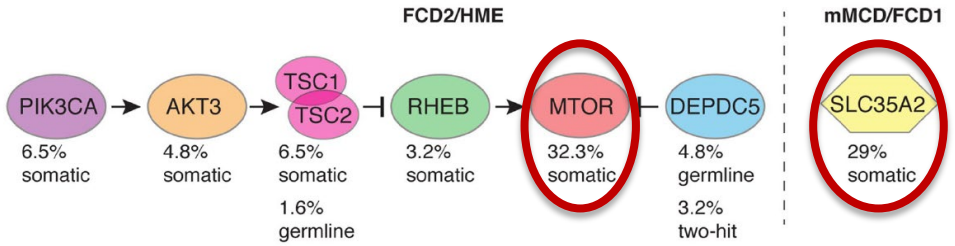
Dissecting the genetic basis of FCD



Framework from monocentric study of children with DRE and MCD (mMCD, FCD 1, FCD2, HME)



63% of FCD2/HME

Baldassari et al., Acta Neuropathol. 138: 885-900, 2019

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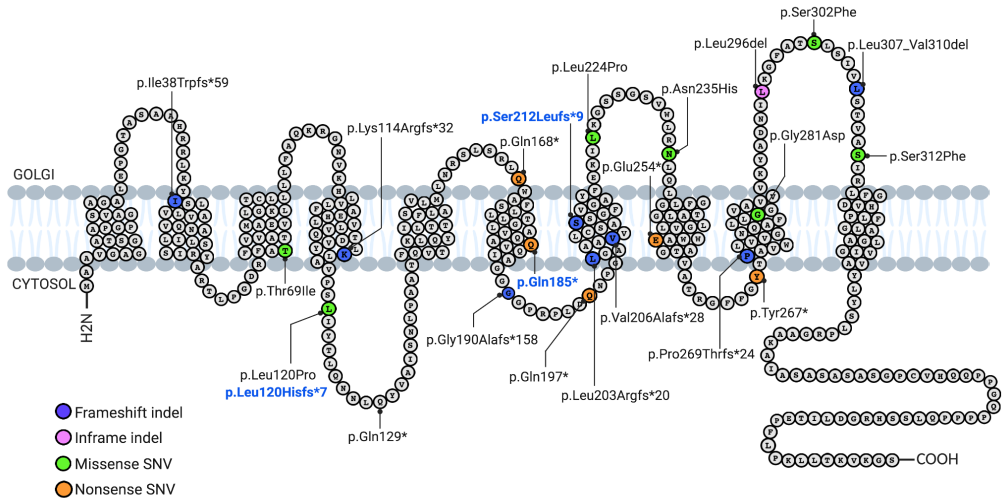
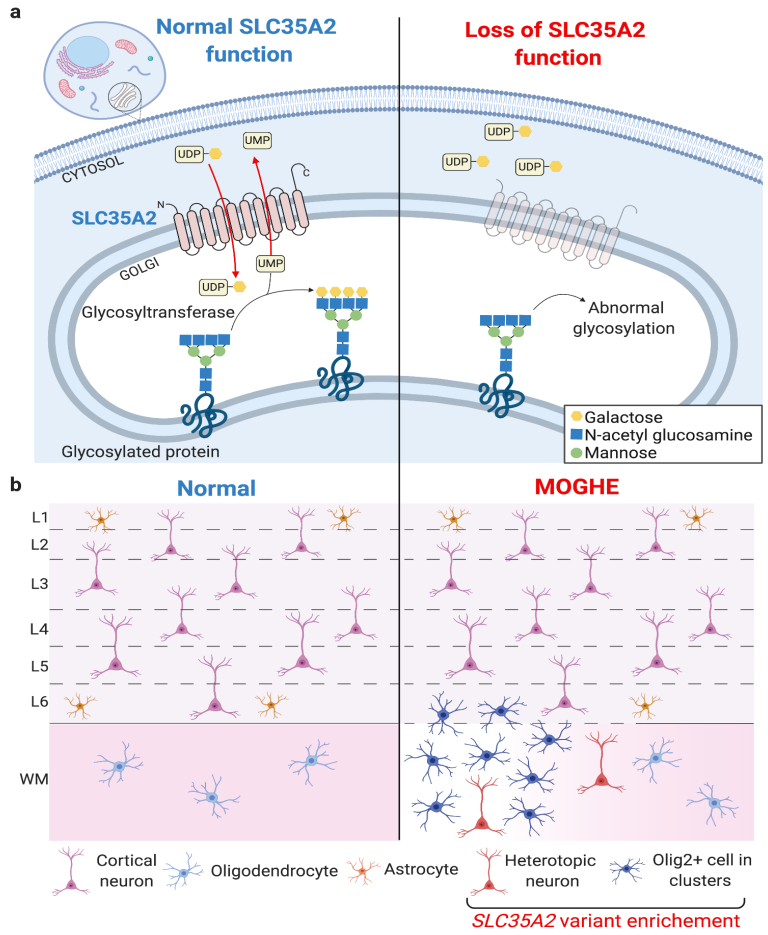
MOGHE: mMCD with proliferative oligodendroglial hyperplasia in epilepsy, SLC35A2 altered

We identified **somatic** pathogenic SLC35A2 variants in 9/20 (45%) patients with mosaic rates ranging from 7 to 52%. We also histopathologically identified MOGHE in 17 cases with previously reported brain somatic SLC35A2 mutations.

SLC35A2 encodes a UDP-galactose transporter.

Germline mutations cause a rare type of congenital disorder of glycosylation.





Bonduelle et al. Acta Neuropathol. Comm. 2021

The ILAE 2022 consensus classification update of Focal Cortical Dysplasia

FCD Type I	**FCD Ia** **vertical microcolumns**	**FCD b** **abnormal layering**	**FCD Ic** **vertical and horizontal abnormalities**	
FCD Type II	**FCD IIa with dysmorphic neurons** *		**FCD IIb** **dysmorphic neurons and balloon cells** *	
FCD Type III	**FCD IIIa** **cortical dyslamination associated with HS**	**FCD IIIb** **cortical dyslamination adjacent to brain tumor**	**FCD IIIc** **cortical dyslamination adjacent to vascular malformation**	**FCD IIId** **cortical dyslamination adjacent to lesion acquired during early life, e.g. stroke**
White matter lesions	**mMCD* with excessive heterotopic neurons**		**mMCD with oligodendroglial hyperplasia in epilepsy (MOGHE)** *	

* **mMCD:** not associated with any other principal lesion, such as hippocampal sclerosis, brain tumor, or vascular malformation.
** **no FCD**: a descriptive report is recommended to highlight anatomical ambiguities (if applicable)
New entities: in green color
Asterisk: FCD with identified brain somatic mosaicism

Najm et al. Epilepsia (in revision)

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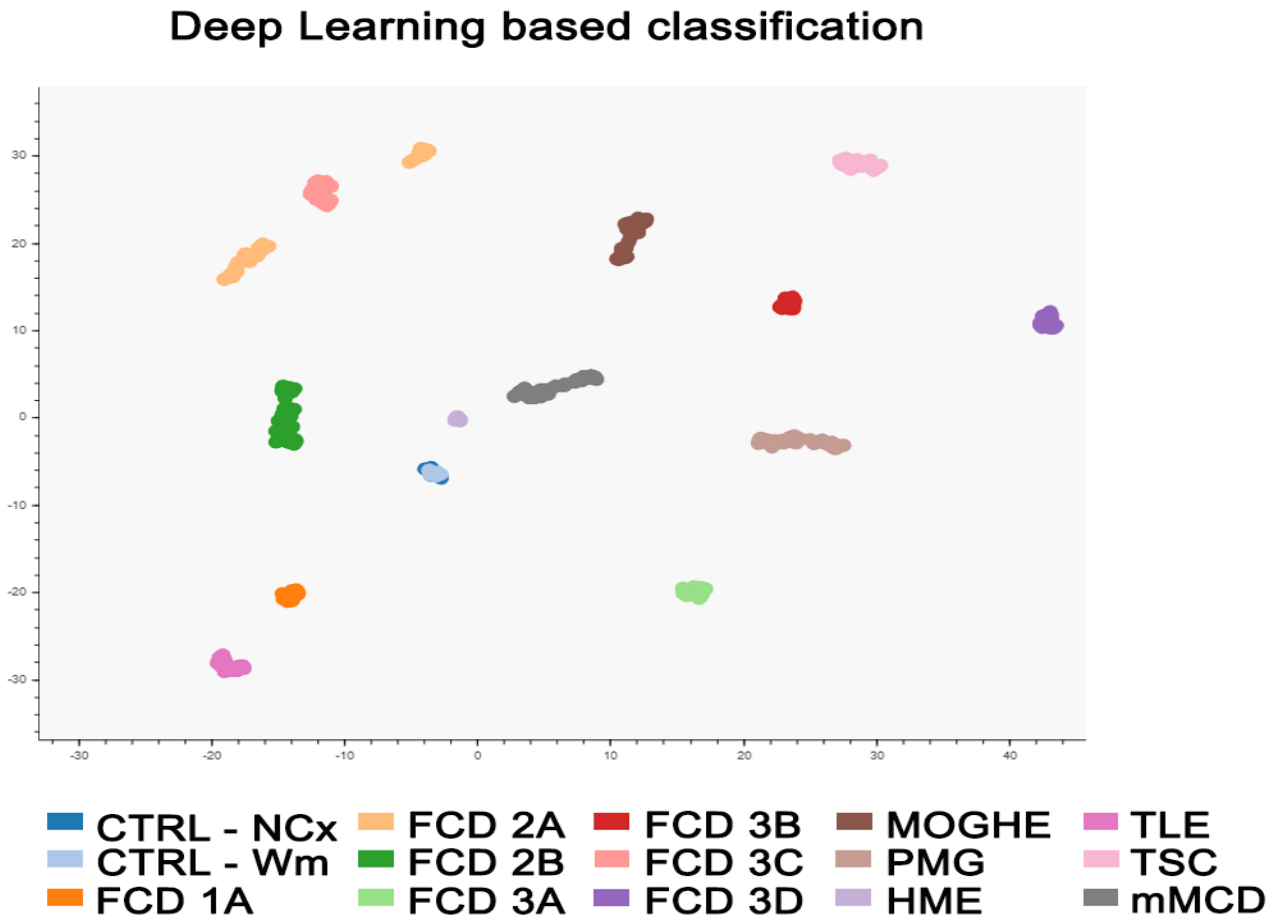
Developing a DNA methylation-based classification of human MCD



Jabari et al. Acta Neuropathologica 2022

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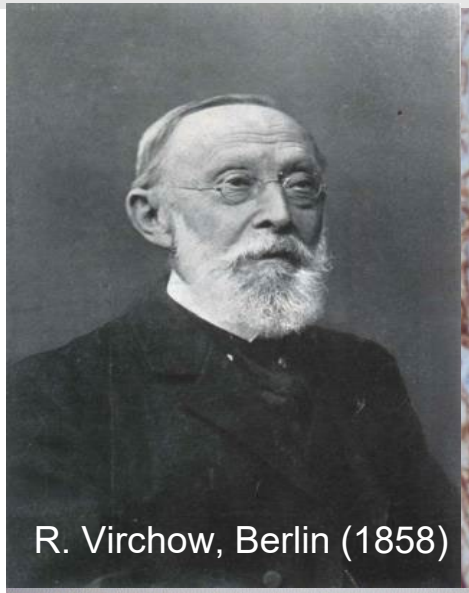
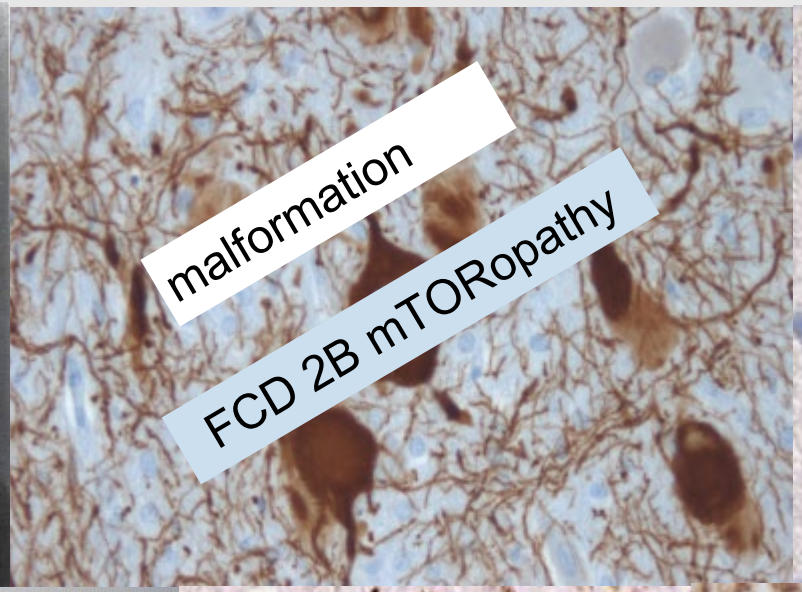
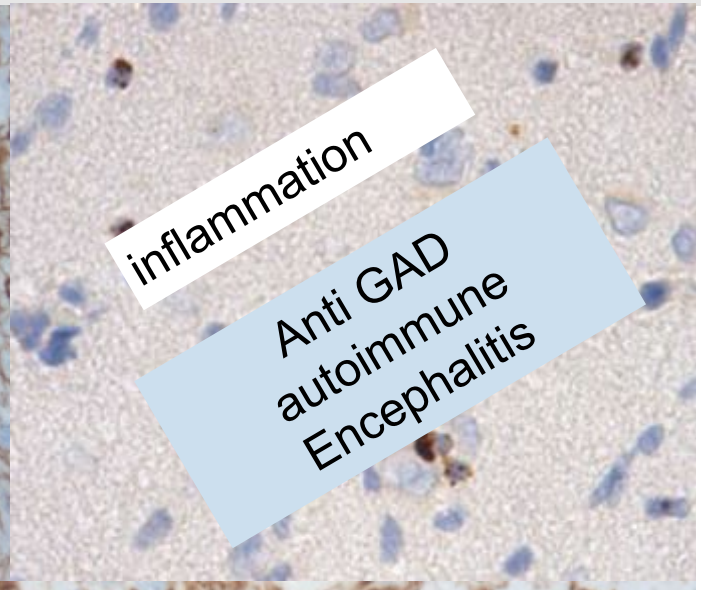
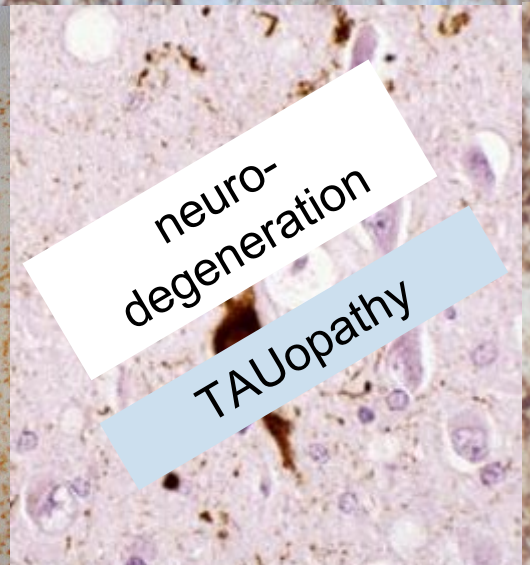
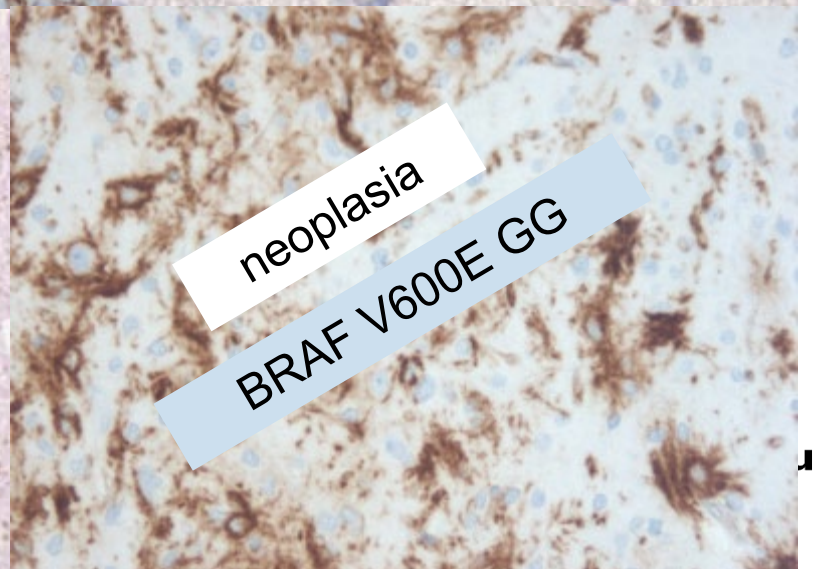
The transition from cellular to molecular pathology and from modern to personalized medicine


R. Virchow, Berlin (1858)









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