

**EDITORIAL**

## An introduction to the mini-symposium on “The Neuropathology of Focal Human Epilepsy”

In May 2012, *Brain Pathology* published a mini-symposium on “etiology of epilepsy,” to update the neuropathology community on common and difficult to diagnose brain lesions associated with early-onset and drug-resistant focal epilepsy and amenable to epilepsy surgery. At this time, epilepsy surgery became widely accepted as a successful treatment option for a carefully selected group of patients and the number of epilepsy surgery centers had been growing continuously. Under the motto “cause matters,” the authors appraised the rejuvenation of neuropathology in the arena of epileptology and its increasing impact for patient selection and postsurgical management. Articles reviewed (i) the concept of low-grade epilepsy-associated tumors, a terminology still used nowadays in the scientific literature (1); (ii) the 1st international consensus classification system for Focal Cortical Dysplasia (FCD), which was just published in 2011 and became the gold standard for diagnosing FCD in clinical practice and research (2); (iii) anticipating an international classification scheme for Hippocampal Sclerosis, published subsequently in 2013 (3); and (iv) the role of the innate and adaptive immune system in epileptic encephalitis.(4) Over the past 9 years, these topics remained in the center of the scientific interest and fascinating discoveries led to a better understanding of the pathogenesis and potentially druggable targets for pharmacological treatment. We are proud, therefore, to present a follow-up mini-symposium on “Neuropathology and Focal Human Epilepsy” and invited a panel of distinguished and highly recognized authors whom were fundamental to these exciting developments. Five topics were chosen to summarize and discuss most current knowledge in epilepsy-associated brain lesions and the quest for best treatment options in epileptology. The discovery of post-zygous brain somatic mosaicism in cortical malformations and their causal role in the pathogenesis of focal brain lesions as well as epileptogenesis, deciphering also their impact at the single-cell level, will be a focus of our mini-symposium, therefore. Other topics of interest cover new diagnostic entities, new molecular diagnostic platforms, and the impact of a reliable neuropathology diagnosis for the prediction of successful postsurgical outcome.

Drs. Blumcke, Cendes, Miyata, Thom, Aronica, and Najm will start this mini-symposium reflecting not only the success of the FCD classification scheme from 2011 (5), but also highlight its gaps and challenges, which will likely result in a timely first update (currently in preparation). They present a series of three case vignettes, each representing a common, although challenging clinical scenario. We will then better understand the need of a comprehensive integration of diagnostic modalities including high-power neuroimaging, advanced EEG recordings, and the neuropathology phenotype–genotype work up to advance clinical patient management to the next level.

The discovery of somatic brain mutations in the MTOR or GATOR signaling pathway causing distinct subtypes of cortical malformations represented a hallmark of scientific research during the past 5 years. Drs. Kobow, Baulac, von Deimling, and Lee describe the currently known genetic landscape of epileptogenic brain lesions and also introduce novel entities defined by their clinicopathological and genetic signature (6). Their review will offer an intriguing insight into DNA methylation analysis, which opened the avenue to “Neuropathology 2.0.” Much was learned from brain tumors and the question remains whether this platform can be translated into the arena of epileptology. In fact, electrical activity transmitted by the epileptic seizures may trigger itself an epigenetically encrypted cellular disease memory and DNA methylation shall be successfully used to differentiate the broad spectrum of cortical malformations in epilepsy.

Drs. Khoshkoo, Lal, and Walsh will continue this path to the exciting area of single-cell genomics, which provides a molecular biological basis to better understand the complex issue of epileptogenic neocortical lesions (7). It is the ever challenging question of (i) which gene is mutated, (ii) in which neuroepithelial cell lineage, (iii) in which region, and (iv) at which time point during neocortical development to produce an epileptogenic and anatomic-pathologically complex lesion.

Drs. Coras, Holthausen, and Sarnat address the challenging issue of Focal Cortical Dysplasia ILAE Type 1 (8). They will reflect on the ongoing discussion how to address the clinico-pathological and genetic spectrum of this disease category at the clinical and scientific level.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2021 The Authors. *Brain Pathology* published by John Wiley & Sons Ltd on behalf of International Society of Neuropathology.

The lack of a specific genetic signature attributed to FCD 1 or its three proposed neuropathology phenotypes, that is, FCD with a vertical, horizontal, or mixed pattern of abnormal cortical neuroanatomy continues to obstruct a reliable disease classification and patient stratification into scientifically sound study groups.

Finally, Drs. Jehi and Braun review postsurgical outcome measures by sharing their experience with large clinical series from Europe and USA (9). It is fair to conclude, that both authors support the concept of early surgery when a lesion can be identified prior to surgery as most successful treatment option until druggable targets will be made available for personalized treatment. However, it is yet to be specified if the histopathology diagnosis and presumptive nature of the lesion also play a role. Our mini-symposium will end with these provocative questions which should alert the international community of neuropathologists to synchronize and foster their efforts toward a comprehensive disease classification integrating histopathology, clinical findings, and genetic studies.

Thus, we wish you a pleasant reading of this mini-symposium with its exciting data collection and provocative theories, which you may find helpful for daily practice, but also to encourage further research and engagement to focal human epilepsies.

Ingmar Blümcke 

*Department of Neuropathology, University Hospital  
Erlangen, Erlangen, Germany*

#### Correspondence

Ingmar Blümcke, Department of Neuropathology,  
University Hospital Erlangen, Schwabachanlage  
6, Erlangen, Germany.  
Email: Ingmar.Blumcke@uk-erlangen.de

#### ORCID

Ingmar Blümcke  <https://orcid.org/0000-0001-8676-0788>

#### REFERENCES

1. Thom M, Blumcke I, Aronica E. Long-term epilepsy-associated tumors. *Brain Pathol.* 2012;22(3):350–79.
2. Aronica E, Becker AJ, Spreafico R. Malformations of cortical development. *Brain Pathol.* 2012;22(3):380–401.
3. Blumcke I, Coras R, Miyata H, Ozkara C. Defining clinico-neuropathological subtypes of mesial temporal lobe epilepsy with hippocampal sclerosis. *Brain Pathol.* 2012;22(3):402–11.
4. Bauer J, Vezzani A, Bien CG. Epileptic encephalitis: the role of the innate and adaptive immune system. *Brain Pathol.* 2012;22(3):412–21.
5. Blumcke I, Cendes F, Miyata H, Thom M, Aronica E, Najm I. Toward a refined genotype–phenotype classification scheme for the international consensus classification of Focal Cortical Dysplasia. *Brain Pathol.* 2021;31:e12956. <https://doi.org/10.1111/bpa.12956>
6. Kobow K, Baulac S, von Deimling A, Lee JH. Molecular diagnostics in drug-resistant focal epilepsy define new disease entities. *Brain Pathol.* 2021;31:e12963. <https://doi.org/10.1111/bpa.12963>
7. Khoshkhoo S, Lal D, Walsh CA. Application of single cell genomics to focal epilepsies: A call to action. *Brain Pathol.* 2021;31:e12958. <https://doi.org/10.1111/bpa.12958>
8. Coras R, Holthausen H, Sarnat HB. Focal cortical dysplasia type 1. *Brain Pathol.* 2021;31:e12964. <https://doi.org/10.1111/bpa.12964>
9. Jehi L, Braun K. Does etiology really matter for epilepsy surgery outcome?. *Brain Pathol.* 2021;31:e12965. <https://doi.org/10.1111/bpa.12965>

**How to cite this article:** Blümcke I. An introduction to the mini-symposium on “The Neuropathology of Focal Human Epilepsy”. *Brain Pathology.* 2021;31:e12975. <https://doi.org/10.1111/bpa.12975>