

Meeting Summary

70th Annual Meeting of the German Society of Neuropathology and Neuroanatomy (DGNN)

Meeting Abstracts

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Sehr geehrte Kolleginnen und Kollegen,

zur Neurowoche 2026 begrüßen wir Sie im Namen der Deutschen Gesellschaft für Neuropathologie und Neuroanatomie herzlich.

Die Neuropathologie hat ihr diagnostisches und wissenschaftliches Spektrum in den vergangenen Jahren deutlich erweitert. Molekulare Tumorklassifikation, Methylierungsdiagnostik, Hochdurchsatzsequenzierung und digitale, KI-gestützte Analyseverfahren sind heute fester Bestandteil unseres Faches und prägen zunehmend klinische Entscheidungen und wissenschaftliche Entwicklungen. Viele dieser Entwicklungen wurden in enger Zusammenarbeit mit den klinischen Neurofächern aufgebaut und weiterentwickelt. Dies betrifft nicht nur die Neuroonkologie, sondern ebenso neurodegenerative, entzündliche und neuromuskuläre Erkrankungen. Die Neuropathologie bewegt sich dabei an der Schnittstelle zwischen Forschung, Diagnostik und klinischer Anwendung. Der enge Austausch mit Neurologie, Neurochirurgie, Neuroradiologie, Neuropädiatrie und den weiteren neurowissenschaftlichen Disziplinen ist hierfür von zentraler Bedeutung.

Gerade deshalb bietet die Neurowoche einen besonderen Rahmen. Sie ermöglicht den fachübergreifenden Austausch und schafft Raum für gemeinsame Diskussionen über neue wissenschaftliche Entwicklungen, diagnostische Konzepte und klinische Herausforderungen. Gerade die interdisziplinäre Zusammenarbeit innerhalb der Neurofächer ist eine wesentliche Voraussetzung, um translationale Entwicklungen in die klinische Anwendung zu überführen. Im neuropathologischen Programm erwarten Sie wissenschaftliche Sitzungen mit aktuellen Entwicklungen aus Diagnostik, translationaler Forschung und experimenteller Neurowissenschaft. Besonders wichtig ist uns dabei auch die Einbindung jüngerer Kolleginnen und Kollegen, die mit neuen wissenschaftlichen und methodischen Impulsen zur Weiterentwicklung unseres Faches beitragen.

Wir freuen uns auf die Diskussionen und den persönlichen Austausch während der Neurowoche 2026.

Mit besten Grüßen

Prof. Dr. Till Acker

Prof. Dr. Christian Mawrin

DGNN-Kongresspräsidenten

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I. Artificial Intelligence

DGNN-WP-68

Free Neuropathol 7:24:4

Meeting Abstract

Deep Learning – Driven Segmentation of Diseased Muscle Fibers

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Background: Spatial omics technologies offer novel opportunities to investigate tissue architecture and molecular organization in situ. However, accurate segmentation of muscle fibers remains a major technical challenge, particularly in pathological conditions where fiber morphology deviates from normal histology. Existing segmentation algorithms are typically trained on structurally preserved tissue and show limited performance in disease contexts characterized by fiber atrophy, angulation, and heterogeneous staining patterns.

Objectives: To develop and validate a robust, disease-aware deep learning workflow for muscle fiber segmentation in human skeletal muscle, enabling improved structural annotation for spatial omics analyses in different myopathies.

Questions:

- (1) Can deep learning-based segmentation models be adapted to accurately detect muscle fibers across a spectrum of pathological conditions?
- (2) Does the inclusion of neuropathologically annotated training data improve segmentation performance in diseased tissue?

Methods: We established a segmentation workflow using human skeletal muscle samples from healthy controls, ME/CFS patients exhibiting type 2B fiber atrophy, and cases of critical illness myopathy, thereby covering a wide range of pathological alterations. A neuropathologically curated training dataset comprising approximately 1,300 images was generated, reflecting diverse morphologies, cell types, and staining conditions. Two deep learning-based models from the Cellpose framework (CellposeSAM and cyto3) were fine-tuned using this dataset to achieve disease-aware segmentation. Model performance was iteratively optimized through training cycles and validated on independent test images.

Results: The curated dataset enabled robust model adaptation to heterogeneous muscle pathology, including atrophic, angulated, and irregularly shaped fibers. Fine-tuned models demonstrated improved segmentation performance across varying disease states compared to baseline configurations, particularly in samples with

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pronounced morphological alterations. The workflow proved applicable to spatial omics datasets, supporting reliable extraction of structural features in both healthy and diseased muscle tissue.

Conclusions: We present a deep learning–based segmentation workflow that improves the accuracy and robustness of muscle fiber detection in pathological skeletal muscle. By incorporating neuropathologically annotated training data, this approach enhances structural characterization in spatial biology applications and facilitates downstream analyses of disease-associated tissue alterations in conditions even with severely affected cytoarchitecture as in critical illness myopathology. The generated dataset provides a valuable resource for future studies aiming to integrate morphology with molecular profiling in neuromuscular disease.

II. Muscle & Nerve

DGNN-WP-23

Free Neuropathol 7:24:6

Meeting Abstract

Human sural nerve biopsies provide insights into pathology and pathophysiology of Charcot-Marie-Tooth neuropathy (CMT-SORD)

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Background: Pathogenic variants in the sorbitol dehydrogenase gene (SORD) are among the most common causes of recessively inherited neuropathies. Histological examinations of homozygous *SORD* knockout rats revealed a significant loss of predominantly large axons, which was particularly pronounced in distal and motor nerves, as well as clusters of regenerating and thinly myelinated axons, isolated circular Schwann cell processes resembling onion bulb formations, and abnormally enlarged (“balloon-like”) myelin sheaths around intact axons.

Objectives: The aim of this study was to systematically and quantitatively examine the histology of human nerves and to correlate the results with clinical course, genotype, nerve conduction studies (NCS), and published animal models.

Questions: Which mechanisms of nerve damage can be detected histologically? Are there histological correlates for the often-slowed nerve conduction velocity observed in NCS? To what extent do biopsy results resemble the histological phenomena observed in KO rats?

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Methods: Five sural nerve biopsies were taken primarily for diagnostic purposes. Patients consented to the scientific use of their samples. The neuropathological examination was performed according to established protocols at a reference center.

Results: At the time of biopsy, the patients (4 male, 2 female) were 26 years old on average (range: 16–47 years). The predominant clinical picture consisted of moderate to severe flaccid distal paresis of the leg muscles, with involvement of the upper extremities in two patients. Sensory symptoms were reported by three patients. NCS revealed a length-dependent, symmetrical, axonal, and predominantly motor neuropathy as the primary manifestation. Histologically, the estimated density of myelinated fibers in the sural nerves was mildly to moderately reduced (mean: 17 %), with a primarily axonal degeneration pattern and a distinct demyelinating component. The number of unmyelinated axons was reduced as well. In all cases, we observed focal intraaxonal accumulations of degenerated organelles and autophagosomes, suggesting progressive axonal damage. A small number of myelin ovoids were likely due to recent degradation of nerve fibers. Similarly, individual clusters of regenerating nerve fibers were found in all nerve samples. In addition, individual nerve fibers with disproportionately thin myelin sheaths were observed.

Conclusions: Our study suggests that both loss of fast-conducting axons and actual demyelination are part of the pathology in CMT-SORD. Myelin abnormalities resembled the findings in the CMT-SORD rat model and in mice with galactose neuropathy. In humans, however, it has not yet been possible to histologically examine motor nerves that are most severely affected clinically. Nevertheless, our cases suggest that due to alterations in sorbitol metabolism and presumed osmotic stress, myelin pathologies also occur in human patients.

DGNN-WP-28

Free Neuropathol 7:24:8

Meeting Abstract

Vasculitic fasciitis characterizes a distinct subset of vasculitic myopathy with interferon-gamma signature

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Background: Vasculitic myopathy (VM) represents a nonspecific manifestation of various vasculitic syndromes that presents with myalgia, leg tenderness, and muscle weakness. Most cases of VM develop in the context of polyarteritis nodosa (PAN), antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, or rheumatoid vasculitis, or manifest as single organ vasculitis. Muscle inflammation in VM is poorly understood, and most studies essentially report the presence of vasculitic changes demonstrated by microscopic analysis of skeletal muscle tissue. However, no detailed characterization or in-depth analyses have been performed so far.

Objectives: The aim of our study was to investigate the phenotype of VM in a homogeneous cohort of ANCA-negative vasculitis based on skeletal muscle biopsy specimens and the retrospective analysis of patient charts.

Questions: What are the morphological and immunological features of VM?

Methods: Multidimensional morphologic (histomorphology, transmission electron microscopy) and immune profiling (quantitative real-time polymerase chain reaction, bulk RNA sequencing) was carried out to clarify the pathophysiology of muscle inflammation in VM.

Results: ANCA-negative VM typically presents with myalgia involving the lower extremities, accompanied by cutaneous manifestations, constitutional symptoms, and marked systemic inflammation. Half of the patients (6/12; 50.0 %) met the classification criteria for ‘classic PAN’. Serum creatine kinase (CK) activity was normal in most cases (10/12; 83.3 %). The presence of skeletal muscle vasculitis was confirmed by histopathology in 9/12

(75.0 %) cases. Specifically, ANCA-negative VM predominantly affected small arteries and was consistently associated with small vessel involvement of the epimysial fascia (9/10; 90.0 %), which was termed 'vasculitic fasciitis' (VF). Signs of necrotizing vasculitis were occasionally noted (3/9; 33.3 %). Mild endomysial fibrosis and muscle fiber necrosis could be compatible with a rather acute disease onset and may account for normal or slightly elevated levels of serum CK activity, respectively. Additionally, nonspecific myopathic changes such as capillary vessel mural thickening and variations of muscle fiber size were detected in all analyzed muscle biopsy specimens. Immunohistochemical studies revealed perifocal sarcolemmal upregulation of major histocompatibility complex class I in the majority of cases (10/11; 90.9 %). RNA sequencing revealed that ANCA-negative VM is characterized by a dominant interferon-gamma-driven immune response, broad cytokine activation including tumor necrosis factor-related genes, and selective upregulation of angiogenesis- and endothelium-associated transcripts.

Conclusions: VF represents a distinct histopathological pattern and possibly a diagnostic lesion associated with ANCA-negative VM that can manifest with signs of fascial inflammation on MRI and likely contributes to localized pain. ANCA-negative VM is characterized by a dominant IFN γ -driven immune response, broad cytokine activation including IL-6, TNF-related genes, and selective upregulation of angiogenesis- and endothelium-associated transcripts.

DGNN-WP-31

Free Neuropathol 7:24:10

Meeting Abstract

Intercellular adhesion molecule 1 (ICAM-1) in muscle and blood is a promising novel biomarker for the diagnosis and monitoring of myositis

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Background: Idiopathic inflammatory myopathies (IIMs) represent a heterogeneous group of autoimmune diseases characterised by immune-mediated muscle fibre damage. An accurate diagnosis is essential for determining the most appropriate treatment plan and prognosis for each patient. In recent years, muscle biopsy has played an increasingly important role in improving diagnostic precision. Intercellular adhesion molecule 1 (ICAM-1) is a key mediator of immune cell adhesion and transmigration. While ICAM-1 expression is limited to endothelial cells in healthy skeletal muscle, it is upregulated in myocytes in myositis. The role of ICAM-1 has not yet been investigated in a larger cohort of patients with IIM.

Objectives: The aim of the study was to establish an automated method of quantifying ICAM1 expression in muscle sections, and to analyse whether ICAM1 could serve as a diagnostic and prognostic marker for myositis and treatment response in muscle biopsies and blood samples.

Methods: A total of 306 muscle biopsies (28 % myositis, 16 % healthy control (HC), 56 % other pathology (OP)) and 146 blood samples (42 % myositis, 15 % HC and 43 % OP) were included. In 109 cases, tissue and blood samples were available from the same patient. ICAM-1 expression was assessed retrospectively on DAB stained whole-muscle sections. The number of positive ICAM-1 pixels per μm^2 (% of total section area) was quantified using digital image analysis (QuPath). Soluble ICAM-1 (sICAM-1) was measured in serum using an ELISA assay.

Results: The expression of ICAM-1 was significantly higher in myositis sections (mean: 36.5 % $\pm$ 26.1 %) than in HC (mean: 5.9 % $\pm$ 4.0 %, $p < 0.0001$) and OP (mean: 5.5 % $\pm$ 4.0 %, $p < 0.0001$). ROC analysis showed a high sensitivity (0.77), specificity (0.93) and area under the curve (AUC, 0.891) for discriminating between myositis and non-myositis muscle sections. sICAM-1 levels were significantly higher in serum of patients with myositis not receiving immunosuppressive therapy (mean: 316 ng/ml $\pm$ 123) than in HC (mean: 244 ng/ml $\pm$ 598.64, $p = 0.0236$). Regression analysis revealed a significant correlation between ICAM1 expression in muscle sections and blood samples from 12 myositis patients not receiving immune-modulating treatment ($r = 0.53$, $p = 0.04$).

Conclusion: ICAM-1 is a promising novel diagnostic marker for myositis in muscle biopsies. The results of our pilot study analysing sICAM-1 in blood samples indicate that sICAM-1 may serve as a diagnostic marker and may be useful for monitoring therapeutic responses in myositis.

DGNN-WP-55

Free Neuropathol 7:24:12

Meeting Abstract

The chaperonin TRiC component Cct3 is required for axonal transport, myelination, and neuromuscular junction refinement

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Background: TRiCopathies are recently discovered neurodevelopmental diseases caused by pathogenic variants in components of the chaperonin tailless complex polypeptide 1 ring complex (TRiC). Composed of chaperonin containing TCP1 subunits 1–8 (CCT1–8), TRiC acts as a chaperone that is required for folding of 10 % of proteome, including actin and tubulin. Patients with TRiCopathies display variable combinations of cognitive impairment, epilepsy, polymicrogyria, white matter reduction, cerebellar hypoplasia and alterations in the peripheral neuromuscular system.

Objectives: Here, we aimed at better understanding the pathophysiological role of Cct3 in neurodevelopment, particularly in myelin formation and the neuromuscular system using zebrafish as a model system.

Questions: We asked whether the observed phenotypes in patients with TRiCopathies are conserved in zebrafish and which mechanisms are involved in the pathophysiology.

Methods: We have generated two CRISPR/Cas9 loss-of-function alleles of the orthologous zebrafish *cct3* gene. By combining these alleles with transgenic lines and immunostainings we visualized different cell types and subcellular structures in the nervous system by confocal microscopy. Furthermore, we performed electron microscopy to examine zebrafish in comparison to human patient-derived tissue.

Results: We demonstrated that *cct3* mutant zebrafish fail to form normal myelin sheaths. This was associated with early apoptotic death of neural crest-derived Schwann cells, which were particularly vulnerable to loss of Cct3 function. In line with the observations in patients, developmental refinement of neuromuscular junctions (NMJ) required Cct3. Furthermore, we observed profound cytoskeletal alterations, in particular of tubulin and microtubules as well as severely disturbed microtubule-dependent axonal transport of organelles in peripheral motor axons. Cct3 displays an essential role in myelination, survival of neural crest-derived cells, NMJ refinement, tubulin and microtubule biology as well as axonal transport.

Conclusions: These data enhance our understanding of the conserved role of Cct3/TRiC in the developing nervous system and the pathophysiological mechanisms in TRiCopathies. Given that axonal transport is essential for transport of axon-glial and signaling factors shaping the NMJ, we speculate that the essential role of Cct3 in axonal transport is a common denominator for the observed phenotypes.

III. Neurodegeneration

DGNN-WP-6

Free Neuropathol 7:24:13

Meeting Abstract

The Enteric Diagnosis of α -Synuclein Aggregation Disorders

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Background: According to Braak's hypothesis, α -synuclein aggregation diseases such as Parkinson disease are triggered by aggregated α -synuclein (α -Syn) in the gastrointestinal tract, which spreads in a prion-like manner to the central nervous system. Consequently, the pathologically misfolded protein should be detectable early and abundantly in enteric tissue, rendering the various parts of the gastrointestinal tract an attractive target for biomarker research.

Objectives: The question arises as to whether these pathophysiological assumptions can be utilized for diagnostic purposes. Our work group set out to determine the optimal biopsy site, minimum biopsy size, and histopathological technique for enteric diagnosis.

Questions: Which sections of the intestine are suitable as diagnostic targets? What is the minimum biopsy size? What diagnostic performance can be achieved after controlling for aggregate load and phosphorylation status?

Methods: Samples were obtained from the esophagus, stomach, duodenum, jejunum, ileum, colon, appendix, and rectum. These specimens had previously been collected during autopsies of 20 patients with either a neuropathologically validated diagnosis of Parkinson disease or Lewy body dementia, as well as 15 cases with atypical parkinsonian disorders or other clinical differential diagnoses. Gold-standard immunohistochemistry was compared with PET blot as an established method in the field of prion and prion-like diseases for highly specific aggregate detection. Antibodies against native and phosphorylated α -syn were used, and varying proteinase pretreatments were compared.

Results: A gradient with at least two peaks was observed, with local maxima in the stomach and ileum. The minimum biopsy size was in the range of more than 30 mm² for most specimens and especially after control for

phosphorylation and aggregation status. A protocol using PET blot and the antibody pSer129 on gastric autopsy specimens achieved a sensitivity of 81 % and a specificity of 92 %.

Conclusions: This study contributes to the search for peripheral biomarkers of α -synuclein aggregation diseases and identifies the stomach and ileum as suitable targets for enteric diagnostics in principle. In addition to targets that have already been researched, such as the submandibular gland and skin biopsies, our protocol offers the option of utilizing resections from the gastrointestinal tract for diagnostic purposes. At the same time, the high minimum biopsy size required for the detection of aggregates and phosphorylation highlights clear limitations of enteric diagnostics for clinical routine.

DGNN-WP-8

Free Neuropathol 7:24:15

Meeting Abstract

Alzheimer's Disease with and without TDP-43 pathology differ in the solubility patterns of the proteome

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Background: Alzheimer's disease (AD) is the leading cause of dementia, neuropathologically characterized by amyloid β (A β) plaques and neurofibrillary tangles consisting of abnormal phosphorylated tau (pTau). In addition, co-pathologies can influence disease progression and complicate both diagnosis and therapeutic intervention. Emerging evidence suggests that TDP-43 co-pathology, also known as limbic-predominant age-related TDP-43 encephalopathy neuropathological changes (LATE-NC), plays a significant role in AD progression.

Objective: To determine the impact of TDP-43/LATE-NC co-pathology on the proteome of AD cases.

Methods: We studied a cohort of well-characterized human post-mortem brains. Samples from the perirhinal cortex (n = 78) and frontal cortex (n = 80) were analyzed. The cohort comprised non-demented controls, asymptomatic, and symptomatic AD cases, with both AD groups stratified by the presence or absence of LATE-NC. Samples underwent sequential centrifugation to generate four physiochemically distinct protein fractions: TBS-soluble, TBS-insoluble (dispersible), SDS-soluble, and formic acid-soluble. By doing so, changes in protein solubility can be identified in addition to simple protein abundance patterns. All samples were analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) with data-independent acquisition (DIA). Differential expression and weighted gene co-expression network analyses were applied to identify proteomic signatures associated with AD+LATE-NC.

Results: A greater overall effect on the AD proteome of AD+LATE-NC cases in comparison to cases without LATE-NC was observed. Additionally, we identified a TDP-43-associated, coordinated protein solubility shift characterized by a region dependent depletion of soluble protein species and enrichment of insoluble protein species. Gene ontology analysis showed these proteins were enriched for pathways related to ubiquitination, the proteasome core complex, and synaptic organization.

Conclusions: The presence of TDP-43 pathology exacerbates the neurodegenerative process in AD presumably by compromising the solubility of many proteins, potentially causing alteration of respective protein functions. Notably, the TDP-43-associated solubility changes were primarily found in ribosomal and proteasomal proteins in both brain regions, suggesting that AD+LATE-NC cases exhibit heightened disruption of molecular pathways crucial for maintaining proteostasis compared to AD cases without LATE-NC. Together, these findings provide a potential mechanistic explanation for the increased aggregation burden reported in AD+LATE-NC cases.

Funding: FWO (Belgium), Alzheimer's Association (USA)

DGNN-WP-41

Free Neuropathol 7:24:17

Meeting Abstract

Detection of α -synuclein aggregates in peripheral tissue biopsies as a biomarker for Parkinson's disease

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Background: The definite diagnosis of Parkinson's disease (PD) is made by the detection of α -synuclein aggregates in the brain *post mortem*. Traces of α -synuclein aggregates in extracerebral tissue biopsies may serve as an appropriate biomarker to confirm a clinical diagnosis *in vivo*. Submandibular gland tissue from PD autopsies contains sufficient amounts of α -synuclein aggregates for detection.

Objectives: We aimed to determine whether detecting of α -synuclein aggregates in salivary gland biopsies is an effective means of diagnosing PD patients.

Methods: We examined the tissues of salivary gland biopsies from patients with clinical Parkinson's disease and their age-matched controls to detect α -synuclein aggregates. We used real-time quaking induced conversion (RT-QuIC) as a seed amplification assay, immunohistochemical detection, and the paraffin-embedded tissue blot (PET-blot) as confirmatory methods.

Results: In the initial analysis, the RT-QuIC assay demonstrated a sensitivity comparable to the clinical diagnosis when neuropathological examination is the gold standard and exhibited a similar level of specificity as the PET-blot method.

Conclusions: RT-QuIC assay on salivary gland biopsies may have the potential to serve as a valuable instrument to improve the diagnosis of PD. Further validation is necessary to substantiate these findings in a large-scale investigation.

DGNN-WP-49

Free Neuropathol 7:24:18

Meeting Abstract

AI-based assessment of thorn-shaped astrocytes in the very elderly (Vantaa 85+)

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Background: Ageing-related tau astrogliopathy (ARTAG), consisting of hyperphosphorylated tau in astrocytes, is common in the elderly. Its clinical significance is yet unclear. The hallmarks of ARTAG are granular/fuzzy and thorn-shaped astrocytes (TSA). TSA can occur in various locations in the grey and white matter. We previously evaluated the presence of ARTAG histologically in the Vantaa 85+ study, a unique population-based cohort, comprising 304 individuals who underwent autopsy, including thorough neuropathological assessment. Histological assessment revealed associations of ARTAG with male sex, limbic-predominant age-related TDP-43 encephalopathy neuropathological changes, hippocampal sclerosis of age, argyrophilic grains and cerebrovascular disease.

Objectives: In addition to a previously conducted study assessing the presence of ARTAG lesions in the oldest old, we aim to quantify TSA in different brain regions by an AI-based algorithm, applying the Aiforia platform.

Questions: By accurate quantification of TSA, we want to further elucidate:

- i) What is the TSA burden in various subregions and how are TSA spatially distributed in the very elderly?
- ii) Can we identify a particular progression pattern?
- iii) Are there differences between the two hemispheres?
- iv) Does the distribution differ between various neuropathological disease groups?

Methods: Eight different brain regions from the medial temporal lobe, neocortex and midbrain were immunohistochemically stained (AT8) and light microscopically inspected for the presence of TSA. Positive samples were scanned and micrographs were uploaded to the Aiforia digital pathology platform (total n = 576). To create an algorithm for the detection of TSA, 75 images were used as training dataset. After the algorithm reached a sufficient level of performance, it was validated independently by three neuropathologists. For the analysis of TSA, regions of interest will be marked and analysed using the Aiforia algorithm. Ultimately, a machine learning approach, such as SuStain modeling, will be tested.

Results: The algorithm created in Aiforia performs well, both for the recognition of brain tissue (total error: 0.04 %, F1 score: 99.98 %) and TSA (total error: 0.72 %, F1 score: 99.64 %). Analysis of individual brain sections is still ongoing.

DGNN-WP-61

Free Neuropathol 7:24:19

Meeting Abstract

Determinants of amyloid beta plaque composition in Alzheimer's disease

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Background: Amyloid beta (A β) deposition, a neuropathological hallmark of Alzheimer's disease (AD), along with hyperphosphorylated tau, accumulates in various forms in the brain. A large-scale overview of different A β plaque types in the human brain, as well as factors influencing and being influenced by them, is lacking.

Objectives: We aim to quantify A β deposition across brain regions in advanced AD cases. Correlations between deposit classes and associations with sex, genotypes, and clinical factors will be assessed. Thereby, we address the heterogeneity of AD and evaluate the clinical significance of specific deposition forms.

Questions: How are different types of A β deposits distributed and correlated with each other? How do sex and ApoE genotype impact the pattern of A β deposition? Which A β deposits are associated with a shorter disease duration?

Methods: The cohort comprises 84 advanced human AD cases with clinical dementia of the Neurobiobank Munich with up to eleven manually annotated cortical regions per case. A β deposits were segmented in 4G8 diaminobenzidine stains with a random forest pixel classifier. Segmented A β plaques were extracted, preprocessed, and classified into six deposit classes (cored, diffuse light, diffuse dense, small dense, compact plaques, and cerebral amyloid angiopathy/CAA) using a convolutional neural network with partial visual validation. To examine links between deposit classes, class densities and proportions were correlated with each other and with total A β deposit loads using Pearson correlation. To investigate the relationships between sex, ApoE genotype, and disease duration with A β classes, multiple linear regression models were applied, correcting for region names, sex, age at death, and ApoE status where appropriate.

Results: Frontal, parietal, temporal and insula cortex showed a median of 82–105 A β deposits/mm², which was significantly higher than in occipital, parahippocampal and entorhinal cortex with median loads of 28–50 deposits/mm². Diffuse light deposits dominated in all cortical regions, followed by small dense, diffuse dense, and compact plaques. All plaque class densities correlated positively with the overall A β deposit load except cored plaques and CAA, which showed no correlation. The densities of diffuse dense, small dense and compact plaques were positively correlated with each other. A higher proportion of diffuse light plaques was negatively correlated with diffuse dense, compact, small dense plaques and CAA.

Female cases presented with higher loads of diffuse light, diffuse dense, compact, and small dense plaques but equal densities of cored plaques and CAA as men. ApoE4 was associated with increased amounts of diffuse dense and small dense plaques in the cortex.

Short disease duration (< 5 years) was associated with higher proportions of cored plaques and CAA than long disease duration (≥ 15 years). Cases with longer disease durations tended to have higher amounts of diffuse light and diffuse dense plaques.

Conclusions: Sex and ApoE4 genotype impact the A β deposition pattern regarding diffuse light, diffuse dense, compact and small dense plaques. Cored plaques stand out due to similar densities across different subgroups and an elevated proportion in AD with a rapid course, suggesting high clinical relevance and potential as a therapeutic target.

DGNN-WP-65

Free Neuropathol 7:24:21

Meeting Abstract

Profiling astrocyte involvement in multiple system Atrophy (MSA)

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Background: Multiple system atrophy (MSA) is a rare, adult-onset, fatal neurodegenerative disorder characterized histologically by α -synuclein-positive inclusions in oligodendrocytes (*glial cytoplasmic inclusions*, GCIs). In addition, we have previously demonstrated that granular, non-fibrillar tau aggregates associated with astrocytes are an invariable feature of MSA and appear to parallel the burden and distribution of α -synuclein pathology. Moreover, single-nucleus RNA-Sequencing (snRNA-Seq) has revealed an increased expression of *MAPT*, the gene encoding tau, in white matter astrocytes from MSA patients compared to controls.

Objectives: As the origin and pathological significance of these astrocyte-associated tau aggregates remain unclear, we sought to further characterize them and to further elucidate the role of astrocytes in MSA.

Methods: We leveraged our yet unpublished snRNA-seq dataset to characterize cell type-specific transcriptional changes in MSA using Gene Ontology (GO), Gene Set Enrichment Analysis (GSEA), high-dimensional weighted gene co-expression network analysis (hdWGCNA) and CellChat to explore potential alterations in intercellular communication. In parallel, we performed immunohistochemical and immunofluorescence staining to independently assess the molecular and spatial features of astrocyte-associated tau pathology.

Results: Following oligodendrocytes, astrocytes exhibited the second highest number of DEGs across the brain regions examined, indicating broad transcriptional alterations. In addition to an aggregation-supporting environment, genes associated with myelination were upregulated, suggesting potentially aberrant activation of myelination-related gene programs in astrocytes. Cell-cell interaction analyses further revealed increased intercellular communication in regions with less pronounced α -synuclein pathology in MSA, whereas in regions with more severe pathology, interaction strength was overall reduced. Notably, increased astrocytic communication was observed in regions with otherwise reduced intercellular communication. In parallel, we further characterized the granular tau aggregates and found that individual tau granules had a mean volume of $0.1 \mu\text{m}^3$, ranging from 0.001 to $100 \mu\text{m}^3$. Of note, higher granule frequency was associated with larger granule

volume, suggesting a degree of structural maturation. Using a total tau antibody for immunofluorescence staining, tau signal was also detected in AT8-negative astrocytes.

Conclusions: Our findings suggest that astrocytes are involved in disease-related processes in MSA, as reflected by broad transcriptional alterations and region-dependent changes in intercellular communication. The presence of granular tau aggregates, together with detectable total tau signal in AT8-negative astrocytes, indicates that these aggregates may, at least in part, derive from endogenous tau that is processed within astrocytes. Although it remains unclear whether these changes represent primary disease-driving mechanisms or secondary reactive responses, our data point to a potential contribution of astrocytes to the molecular pathology of MSA.

IV. Neuroinflammation

DGNN-WP-69

Free Neuropathol 7:24:23

Meeting Abstract

Neuroimmune and Metabolic Alterations in Post-COVID Syndrome and ME/CFS

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Background: Post-COVID condition (PCC), frequently overlapping with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), is characterized by persistent neurological and systemic symptoms. Increasing evidence suggests involvement of neuroimmune dysregulation and metabolic alterations, yet the underlying mechanisms remain poorly understood.

Objectives: The SERIMM consortium aims to comprehensively characterize neuroimmune and metabolic alterations in PCS and PCS ME/CFS through multimodal analyses integrating clinical cohorts, cerebrospinal fluid (CSF), blood-based omics, spatial transcriptomics, and animal models.

Questions:

- (1) Are PCS and PCS ME/CFS associated with alterations in pathways of central and peripheral serotonin metabolism?
- (2) Do these conditions exhibit signatures of sustained neuroimmune activation?
- (3) Can multimodal molecular profiling and adapted animal models identify disease-specific pathways and potential biomarkers?

Methods: A prospective PCS cohort and a retrospective longitudinal cohort (n = 40) were established. In addition, a CSF cohort (n = 150; including PCS, inflammatory, and control samples) was assembled. Metabolites and Proteins in CSF and blood were quantified using liquid chromatography–mass spectrometry (LC-MS). Single-

nucleus RNA sequencing (snRNA-seq) of skeletal muscle (n = 16) and spatial transcriptomics of post mortem brain stem tissue were applied to assess cell-type-specific and spatial immune activation. SARS-CoV-2 animal models (mice and hamsters) were used to investigate behavioral and molecular changes over time. Advanced image analysis approaches were implemented for tissue characterization.

Results: LC-MS analysis of CSF revealed alterations in tryptophan metabolism in PCS, including a reduced serotonin-to-tryptophan ratio and increased kynurenine pathway metabolites, indicating a shift toward inflammation-associated metabolic pathways. In peripheral blood, serotonin levels were strongly influenced by SSRI treatment, while PCS ME/CFS patients showed distinct alterations in indole metabolism, suggesting a potential link to microbiome-associated pathways. Proteomic analyses identified changes in synaptic and innate immune pathways in PCS ME/CFS in line with spatial transcriptomics demonstrating activation of the innate immune system, particularly in perivascular niches, with microglia-like cells exhibiting a macrophage-associated phenotype (e.g., increased CD74, ITGAX, CD14 and reduced P2RY12 expression). Animal models confirmed persistent behavioral alterations beyond the acute phase of infection, accompanied by ongoing molecular changes.

Conclusions: PCS and PCS ME/CFS are associated with sustained neuroimmune activation and significant alterations in tryptophan metabolism, particularly a shift toward the kynurenine pathway in the central nervous system. Multimodal analyses indicate that these changes involve both central and peripheral compartments and may be modulated by external factors such as medication. Ongoing integrative analyses aim to link molecular signatures with clinical phenotypes and to identify potential biomarkers and therapeutic targets.

V. Tumor

DGNN-WP-32

Free Neuropathol 7:24:25

Meeting Abstract

Deciphering the molecular granularity of subependymomas and its distinction from posterior fossa ependymoma

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Background: The current CNS tumor classification of the WHO currently subsumes subependymomas (SE) of the supratentorial, infratentorial, and spinal compartment as a single tumor type. Molecular data on SE are generally sparse, but SE are known to exhibit distinct global DNA methylation profiles according to their anatomical location. Apart from this epigenetic heterogeneity, previous studies indicate that a fraction of posterior fossa tumors exhibiting DNA methylation profiles of SE morphologically appear as ependymomas and may demonstrate a relapsing disease.

Objective: A thorough molecular investigation of these understudied types of ependymomas and subependymomas should provide a basis for an improved diagnostic process.

Method: We assembled a cohort of ependymally and subependymally differentiated tumors that best match supratentorial (n = 89), infratentorial (n = 146), or spinal (n = 45) SE DNA methylation profiles.

Results: Infratentorial tumors occurred at significantly higher ages and with a male to female ratio of 4:1. Furthermore, infratentorial tumors with an SE DNA methylation profile displayed two distinct subtypes, with one of them (n = 49) being highly enriched for tumors that morphologically appear as ependymomas. These ependymomas carry a loss of chromosome 6 as well as *TERT* promoter mutations, and respective patients are significantly older while displaying a significantly shorter progression-free survival (5-year PFS of 72.85 % (95 % CI, 56.08 % to 94.64 %), compared to 93.09 % (95 % CI, 84.22 % to 100 %) for posterior fossa SE, p = 0.00014). Supratentorial SE featured losses of chromosome 8, while a subset of tumors presented with a distinct DNA methylation profile and a chromothripsis-like segmentation of chromosome 6. Such chromosomal abnormalities were similarly observed in spinal SE, which was the least frequent type of SE in our series.

Conclusion: Taken together, we demonstrate that SE of different anatomical compartments differ by global DNA methylation pattern as well as copy number changes. Furthermore, DNA methylation profiling may help to distinguish SE from a type of infratentorial ependymomas that frequently shows relapses, but is distinct from PFA and PFB ependymomas and was therefore provisionally named PFC. These findings are likely to have implications for future classification and grading schemes of ependymal tumors.

DGNN-WP-38

Free Neuropathol 7:24:27

Meeting Abstract

Pituitary neuroendocrine tumor or pituitary adenoma? Let's ask the epigenome!

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Background: The introduction of the term pituitary neuroendocrine tumor (PitNET) to replace pituitary adenoma has sparked a versatile debate among experts. The controversy surrounding this nomenclature change includes the question whether these tumors' biological identity truly corresponds to neuroendocrine tumors.

Objective: In this meta-analysis, DNA methylation data were interrogated to clarify whether the old or new nomenclature more accurately reflects the epigenome of these tumors.

Methods: Publicly available DNA methylation data of 100 NETs, 100 PitNETs/adenomas and 100 adenomas of various origins and lineages were compiled from 18 different publications. Epigenomic signatures characteristic of NETs and adenomas were defined and compared to those of PitNETs/adenomas. Promoter CpG methylation levels were investigated for hallmarks of cellular differentiation.

Results: Comparative DNA methylation analyses demonstrated that all 100 PitNETs/adenomas aligned more closely with NETs than with adenomas. Focusing on promoter-associated CpGs moreover confirmed robust epigenomic features associated with neuroendocrine differentiation in PitNETs/adenomas.

Conclusions: PitNETs/adenomas resemble NETs rather than adenomas on the epigenomic level. These findings support PitNET as the biologically more accurate term. Of note, appropriately addressing the broad spectrum of clinical behaviors in these tumors remains a critical issue of the current pituitary tumor classification framework and nomenclature.

DGNN-WP-39

Free Neuropathol 7:24:28

Meeting Abstract

Advancing methylation-based brain tumor classification through Nanopore sequencing data of cerebrospinal fluid-derived cell-free DNA

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Background: Central nervous system (CNS) tumors require precise molecular diagnosis to optimize surgical strategies and targeted therapies. Currently, global DNA methylation profiling of surgically resected tumor tissue is considered the gold standard for CNS tumor classification. However, tumor location in inaccessible regions, high surgical risk, or lack of therapeutic benefit can limit the applicability of this method. Liquid biopsy has emerged as a minimally invasive alternative to detect tumor-derived biomarkers from bodily fluids. Nanopore sequencing of cell-free DNA (cfDNA) isolated from cerebrospinal fluid (CSF) enables rapid analysis of copy number variations (CNVs) and methylation-based classification of CNS tumors.

Objectives: In CSF, classification is often limited by sparse sequencing data due to the low abundance of circulating tumor DNA (ctDNA), and existing algorithms are primarily designed for the analysis of tumor tissue.

Methods: Here, we introduce NanoFlux, an ensemble model designed for the classification of common brain tumors based on Nanopore-sequenced cfDNA isolated from the CSF. NanoFlux was trained using an array-based reference dataset comprising 3,871 tumor tissue samples and validated on a cohort of 140 Nanopore-sequenced cfDNA samples. Further validation was conducted on an independent real-world clinical cohort of 74 patients with imaging-suspected brain tumors. After pre-operative CSF analysis, all patients underwent tissue biopsies with neuropathological work-up.

Results: In the validation cohort, accurate tumor classification was achieved in 78/127 (61.4 %) cases with no misdiagnoses. NanoFlux was benchmarked against three established algorithms, which correctly classified at most 56/127 (44.1 %) samples. Applying NanoFlux, preoperative detection of tumor DNA, including potential copy number alterations, was possible in 20/60 (33.3 %) of cases in patients with an afterwards-confirmed CNS tumor. Correct tumor class prediction via global DNA methylation profiling was achieved in 13/60 (21.7 %), whereas the three benchmarked models correctly classified at most 5/60 (8.5 %) samples. 14 cases (18.9 %) of the cohort did not demonstrate tumor presence by tissue work-up, which was predicted in all cases by Nanopore sequencing of the CSF using NanoFlux.

Conclusions: In summary, NanoFlux demonstrates an improved methylation-based classification of nanopore-sequenced cfDNA isolated from CSF, highlighting the potential of CSF-based liquid biopsy for routine molecular diagnostics in CNS tumors.

DGNN-WP-43

Free Neuropathol 7:24:30

Meeting Abstract

Primary Mismatch Repair Deficient Glioma (PMMRDG), IDH-wildtype and H3-wildtype: A Giant Cell Tumor with Potential for Long-Term Survival Occurring at all Ages

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Background: Replication repair deficiency is associated with an increased risk of developing malignant gliomas. Tumors arising in this context often exhibit characteristic features such as multinucleated giant cells and a high mutational burden. However, clear criteria for reliably distinguishing these tumors from other glioma subtypes remain lacking, and their molecular and clinical characteristics, particularly in adults, are still not well defined.

Objectives: The aim of this study was to investigate primary mismatch repair deficient gliomas (PMMRDGs), a group of IDH-wildtype and H3-wildtype gliomas that is enriched among patients with CMMRD and Lynch syndrome.

Questions: Do PMMRDGs constitute a distinct molecular subgroup of gliomas? What are the defining epigenetic, genetic, and histopathological features of PMMRDGs? Are there specific factors associated with clinical outcomes and survival in patients with PMMRDGs?

Methods: We performed a comprehensive analysis of PMMRDGs (total n = 252), including DNA methylation profiling, assessment of genomic alterations, histopathological evaluation, and immunohistochemical analysis of mismatch repair (MMR) protein expression. Clinical data (n = 108) were analyzed to assess patient outcomes, and findings were validated in an independent reference cohort from the IRRDC consortium.

Results: PMMRDGs were identified across a broad age spectrum, including pediatric, adolescent, and elderly patients. DNA methylation analysis revealed two closely related clusters (pedRTK1a and HGG_E). Tumors in these clusters were characterized by a high frequency of replication repair deficiency. Histopathological examination frequently demonstrated multinucleated giant cells, while immunohistochemistry showed loss of MMR (MLH1, MSH2, MSH6, PMS2) protein expression. Survival analysis indicated that patients with a high mutational burden (> 50 mutations/Mb) and an intact chromosome 9p region often showed long-term survival. This association was confirmed in an independent cohort.

Conclusions: PMMRDGs represent a distinct subgroup of IDH-wildtype gliomas with unique molecular and histopathological features. Importantly, a subset of patients shows potential for long-term survival, likely driven by high mutational burden and associated immune activation. These findings have implications for classification and may inform future therapeutic strategies.

DGNN-WP-53

Free Neuropathol 7:24:31

Meeting Abstract

A subgroup of High-grade gliomas with pleomorphic and pseudopapillary features (HPAP) is characterised by recurrent whole-chromosome losses and frequent alterations in *MEN1*

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Background: High-grade glioma with pleomorphic and pseudopapillary features (HPAP) is a recently described entity which was first identified in a cohort of 31 cases. It is characterised by recurrent loss of chromosome 13 and frequent *TP53* mutations, and is associated with comparatively prolonged overall survival.

Objectives: We identified a cohort of 54 patients with tumours that fulfill the histological and epigenetic criteria for HPAP. This group was initially recognised by us because many cases had been diagnosed as glioblastoma but showed markedly prolonged survival. In addition, these tumours exhibited recurrent whole-chromosome copy number losses across multiple chromosomes, not limited to chromosome 13. We aimed to more clearly define the shared molecular features of this group within HPAPs, which are characterised by widespread chromosomal losses.

Methods: We assessed histology for n = 18 cases. DNA methylation data were analysed for class assignment, copy number variation profiling and mean methylation levels. Tumour samples were further subjected to DNA and RNA sequencing. Clinical follow-up data were retrospectively available for 23 patients.

Results: Median age in our cohort was 51.8 years at biopsy (range: 19 to 76 years). Most tumours exhibited pleomorphic morphology, frequently with pseudopapillary features. Histological features of anaplasia, including necrosis, microvascular proliferation, and increased mitotic activity (≥ 2.5 mitoses/mm²), were observed in 10/18 cases (56 %). Among 30 sequenced cases, 10 tumours (33.3 %) harboured *MEN1* alterations. Notably, two patients had a confirmed diagnosis of multiple endocrine neoplasia type 1 (MEN1), a hereditary cancer predisposition syndrome, and several others presented with multiple extra-CNS/extra-axial tumours in addition to their primary brain lesion. The copy number variation profile was characterised by aneuploidy involving chromosomes 10–15, 17, and 18. We furthermore assessed mean methylation levels of our group as MEN1 is known to interact with KMT2A, and observed increased global mean methylation levels compared to tumour samples assigned to the methylation class mesenchymal glioblastomas and pleomorphic xanthoastrocytomas. Despite their anaplastic histology, patients demonstrated prolonged overall survival (median survival rate: 13.7 years) compared to those with glioblastoma or pleomorphic xanthoastrocytoma, CNS WHO grade 3.

Conclusions: A subgroup within HPAPs characterised by aneuploidy involving chromosomes 10–15, 17, and 18 frequently harbour *MEN1* alterations and may also arise in patients with MEN1 tumour syndrome. They are associated with comparatively favorable clinical outcomes, making accurate distinction from glioblastoma, a common differential diagnosis, especially important.

DGNN-WP-66

Free Neuropathol 7:24:33

Meeting Abstract

iPredict.iGlio: An integrated prognostic framework for IDH-mutant gliomas: First interim analysis of DNA methylation-derived survival prediction

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Background and Objectives: Histopathological grading of IDH-mutant gliomas remains central to clinical risk assessment, yet interobserver variability and heterogeneous clinical outcomes limit prognostic accuracy. With the recent approval of IDH inhibitor monotherapy, refined individual risk stratification has become even more clinically relevant. DNA methylation profiling has transformed brain tumor classification, but its prognostic potential on an individual patient basis is not yet fully explored. iPredict.iGlio addresses this gap by developing an integrated, prognostic framework for IDH-mutant gliomas. Here we present a first interim analysis, investigating whether a methylation-array-derived copy number burden score as well as an integrated deep learning-based framework stratifies survival across institutions.

Methods: Copy number profiles were derived using CGHcall and conumee packages and Fraction of Genome Altered (FGA) metrics for all CNAs as well as for gain and loss categories, separately were determined. A discovery cohort of 120 IDH-mutant gliomas (n = 71 astrocytomas, n = 49 oligodendrogliomas) with DNA methylation data and matching clinical follow-up was assembled. Univariable and multivariable Cox regression models were calculated for overall and progression-free survival with clinical and histological parameters. First external validation was carried out in five independent validation cohorts with available PFS or OS data. A deep learning model was trained on methylation array data and matched clinical follow-up from over 800 IDH-mutant glioma samples across multiple cohorts to generate individualized survival predictions.

Results: In the astrocytoma discovery cohort, total FGA was strongly and independently associated with PFS (HR 2.47, 95 % CI 1.67-3.64; p < 0.001), with comparable signals for gain (HR 1.97, 1.43-2.71; p < 0.001) and loss FGA (HR 1.95, 1.33-2.87; p = 0.002). Focal amplification fraction (HR 1.42; p = 0.054) and complete loss FGA (HR 1.51; p = 0.088) showed weaker effects. FGA correlated with methylation clusters and recurrent copy number gains were enriched in high-burden astrocytomas, which was reproducible across all external validation cohorts. Oligodendrogliomas did not show the survival differences we found for astrocytomas. As a first proof-of-concept, the integrated deep learning model showed signals of individual survival stratification.

Conclusions: This first interim analysis of iPredict.iGlio establishes an array-derived copy number burden score (FGA) as a robust survival predictor in IDH-mutant astrocytomas. Interestingly, in oligodendrogliomas the burden score did not show a prognostic value, reflecting the biological and genetic differences of these entities. The score will be validated in larger datasets and integrated as an input into the methylation-based individualized survival prediction frameworks currently in development.

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Meeting Abstract

Changes of Chromatin Conformation Accompanying Malignant Progression in IDH-Mutant Glioma

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Background and Objectives: Isocitrate dehydrogenase (IDH)-mutant gliomas are subtypes of primary brain tumors. They comprise 1p/19q-codeleted oligodendroglioma, CNS WHO grade 2 and 3 and 1p/19q-intact astrocytomas, grades 2 to 4. Both glioma subtypes differ from each other by distribution of activating and repressive histone modification marks. Neither glioma subtype can be curatively resected, thus systemic treatment is crucial for clinical disease management. Yet disease courses are majorly influenced by malignant progression of IDH-mutant gliomas. Even though many studies shed light on genomic alterations fueling malignant behaviour, these mechanisms are far from being well understood.

Methods: To investigate potential changes of the chromatin conformation accompanying malignant progression, we leveraged DNA methylation data of up to 250 IDH-mutant gliomas and used both in silico and immunohistochemical approaches to correlate DNA methylation with histone modification signatures.

Results: We found Latent Methylation Components (LMCs) to dynamically change in higher- vs. lower-grade gliomas while in parallel being specific for each glioma subtype. The LMCs associated with higher-grade gliomas

showed characteristic patterns of DNA hypo- and hypermethylation across the chromatin landscape like CpG sites associated with bivalent promoters and enhancers as well as flanking promoters in detail.

Conclusions: Epigenetic changes frame gliomagenesis and tumor progression. With this study we aim to decipher alterations of higher order chromatin arrangement to improve our knowledge about mechanisms of malignant progression and find epigenetic biomarkers for refined grading.
