

ABSTRACT A1**Investigations of the functional interactions between CIC and ATXN1L in Oligodendroglioma***D. Wong, V. Leblanc, S. Chittaranjan, M. Marra, S. Yip*

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Oligodendroglioma (ODG) is a subtype of low grade glioma marked by unique clinical and genomic characteristics including slow predictable progression, IDH mutation, and 1p19q-codeletion. ODGs are more sensitive to treatment leading to a favorable prognosis. Recently, mutations in CIC, a gene found on chromosome 19q, have been found in up to 70% of IDH mutated, 1p19q-codeleted ODGs. The high frequency of CIC mutations in a hemizygous state indicates that loss or altered function of the CIC protein may be crucially associated with the unique biology of ODG. Previous studies of CIC have shown this protein to be a transcriptional repressor of ETS transcription factors and a negative regulator of the MAPK pathway. CIC and ataxin-1-like (ATXN1L) are also closely involved in the pathology of spinocerebellar ataxia (SCA). However, their relationship and role in brain tumour biology has yet to be elucidated. In this study, we explore the molecular, proteomic, and functional relationship between CIC and ATXN1L which may lead to unique insights on the clinical behavior of ODG as well as identify potential molecular therapeutic targets in this enigmatic brain tumour.

ABSTRACT A2**Adult IDH-wildtype high-grade gliomas with ATRX loss : A case series***Ana Nikolic¹, John J. Kelly², Leslie E. Hamilton¹*¹Division of Neuropathology, Foothills Medical Centre, University of Calgary; ²Department of Neurosurgery, University of Calgary

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Recent genomic advances have led to routine use of ATRX and IDH immunohistochemistry for glioma classification. Three adult patients (age range: 48-52 years) presented with focal neurological symptoms and intra-axial frontal mass lesions. Imaging features were atypical, and unusual features in two cases resulted in repeat imaging and diagnostic delay. On biopsy, all three were high-grade astrocytomas, but with variable histology, including pure GBM-PNET, and two anaplastic astrocytomas, one with gemistocytic features. All cases had diffuse ATRX loss by immunohistochemistry, strong diffuse nuclear TP53 positivity and MGMT promoter methylation. Immunohistochemistry and mutation analysis by SNaPshot single-nucleotide extension PCR for IDH1/2 mutations was negative. A SNaPshot assay revealed the G34R mutation in H3F3A in two cases. Mutations in H3F3A G34R were initially described in pediatric hemispheric high-grade gliomas, but this case series highlights that they may also be seen in older adults. While the prognostic significance of G34R mutations in adult glioma is unknown, testing should be strongly considered in any high-grade glioma with ATRX loss and wild-type IDH.

ABSTRACT A3**Epigenetic landscape in IDH1 mutant glioma***Luolan Li¹, Sitanshu Gakkhar², Misha Bilenky², Annaick Carles¹, Alireza Heravi-Moussavi², Stephanie Cho², Baljit Kamoh², Angela Tam², Richard Moore², Andy Mungall², Steven Jones², Marco Marra², Stephen Yip³, Martin Hirst^{1,2}*¹Department of Microbiology and Immunology, Michael Smith Laboratories, University of British Columbia, Vancouver, BC, V6T 1Z4, Canada; ²BC Cancer Agency Canada's Michael Smith Genome Science Center, Vancouver, BC, V5Z 4S6, Canada;³Department of Pathology and Laboratory Medicine, Vancouver General Hospital, Vancouver, BC, V5Z 1M9, Canada

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Somatic mutations in isocitrate dehydrogenases 1 (IDH1) have been identified as putative drivers in gliomas, and have profound impact on the epigenome by inhibiting α -ketoglutarate-dependent dioxygenases, including Tet and histone demethylases. To understand the role of IDH mutations in tumorigenesis, we profiled the epigenomes of IDH mutant gliomas and neural progenitor cells (NPCs). Compared to NPCs, IDH mutant gliomas showed a global increase in DNA methylation enriched in CpG islands. Surprisingly, for promoter hypermethylated regions associated with differentially expressed genes, only 46% were down-regulated, enriched in Frizzled proteins in Wnt pathway. Among the promoter hypermethylated and upregulated genes, 22% were also associated with loss of H3K27me3, and 21% with gain of H3K27ac. These genes were enriched in neurogenesis, including key transcription factors in neuronal differentiation such as LHX5. In addition, we found hypomethylation highly enriched in enhancers. These enhancers were enriched for binding sites of neuronal differentiation regulators, such as ASCL1 and OLIG2, both were up-regulated in IDH mutant gliomas and activated genes that promotes cell proliferation.

ABSTRACT A4**Tumefactive MS, sentinal lesion, and PCNSL : a diagnostic conundrum***Edward Johnson*

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Distinction between tumefactive MS and sentinel lesion of PCNSL poses a diagnostic conundrum, as exemplified in this report of a 46-year-old man who presented with partial complex seizures, prompting a right temporal resection. Multiple cerebral lesions were detected by MRI 41/2 years later, necessitating a biopsy, after which he developed a brainstem syndrome. Over the 3 years thereafter, three severe relapses occurred referable to transient lesions in the cerebrum (one lesion biopsied), brainstem, and cerebellum. Presumptive diagnosis was tumefactive MS with control by combination of immunosuppressive/modulatory therapies. Emergence of an enlarging left cerebellar mass precipitated death.

Different facets of an inflammatory demyelinating process were demonstrated in the resection specimen and biopsies.