LGG-33. ISOMORPHIC DIFFUSE GLIOMA HAS RECURRENT GENE FUSIONS OF *MYBL1* OR *MYB* AND CAN BE DISTINGUISHED FROM OTHER *MYB/MYBL1* ALTERED GLIOMAS BASED ON A DISTINCT MORPHOLOGY AND DNA METHYLATION PROFILE

Annika K. Wefers[1,2], Damian Stichel[1,2], Daniel Schrimpf[1,2], Felix Sahm[1,2], Andreas von Deimling[1,2], Ingmar Blumcke[3], David T.W. Jones[4,5], and David Capper[6]; [1]Institute of Pathology, Department of Neuropathology, University Hospital Heidelberg, Heidelberg, Germany, [2]German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Clinical Cooperation Unit Neuropathology, Heidelberg, Germany, [3]Department of Neuropathology, University Hospital Erlangen, Erlangen, Germany, [4]Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany, [5]German Cancer Research Center (DKFZ), Pediatric Glioma Research Group, Heidelberg, Germany, [6]Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Department of Neuropathology, Berlin, Germany

Isomorphic diffuse glioma (IDG) was first described in 2004 as an epilepsy-associated supratentorial diffuse glioma with low cellularity, low proliferation and very monomorphic tumour cells. Most patients had seizures since childhood but were operated on as adults. To study the position of these lesions among brain tumours we histologically, molecularly and clinically analysed 26 histologically typical IDGs. Tumour cells were GFAP-positive, MAP2-, OLIG2- and CD34-negative and the nuclear ATRX-expression was retained. Proliferation was very low. Sequencing of 24 cases revealed an IDH-wildtype status. Cluster analyses of DNA methylation data showed that IDG has a DNA methylation profile distinct from those of different glial/glio-neuronal brain tumours and normal hemispheric tissue. About half of IDGs had copy number alterations of *MYBL1* or *MYB* (13/25) and half of the cases analysed by RNA-sequencing had gene fusions of *MYBL1* or *MYB* with various gene partners (11/22), often associated with an increased RNA-expression of the respective *MYB*-family gene. Integrating all data available, 77% of IDGs had either *MYBL1* (54%) or *MYB* (23%) alterations. All patients had a good outcome and most were seizure-free after surgery. In summary, we show that isomorphic diffuse glioma is a distinct benign tumour in the family of *MYB/MYBL1*-altered gliomas. DNA methylation analysis is very helpful for their identification. More recent analyses of a large cohort of *MYB/MYBL1*-altered brain tumours suggest the presence of a third methylation group that primarily contains paediatric cases and seems to be distinct from IDG and angiocentric gliomas. Further histological, molecular and clinical analyses are ongoing.

LGG-34. CLINICAL AND MOLECULAR CHARACTERIZATION OF A MULTI-INSTITUTIONAL COHORT OF PEDIATRIC SPINAL CORD LOW-GRADE GLIOMAS

Sydney Grob[1,2], Lianna Nobre[3], Kurtis Davies[1], Scott Ryall[3], Dara Aisner[1], Lindsey Hoffman[4], Shadi Zahedi[1,2], Andrew Morin[1,2], Anandani Nellan[1,2], Adam Green[1,2], Nicholas Foreman[1,2], Rajeev Vibhakar[1,2], Todd Hankinson[1,2], Michael Handler[1,2], Cynthia Hawkins[3], Uri Tabori[3], BK Kleinschmidt-DeMasters[1], and Jean Mulcahy Levy[1,2]; [1]University of Colorado Denver, Aurora, CO, USA, [2]Morgan Adams Foundation Pediatric Brain Tumor Program, Aurora, CO, USA, [3]Hospital for Sick Children, Toronto, ON, Canada, [4]Phoenix Children's Hospital, Phoenix, AZ, USA

BACKGROUND: The MAPK/ERK pathway is involved in cell growth and proliferation, and mutations in the *BRAF* paralog of this pathway have made it an oncogene of interest in pediatric cancer. Previous studies have identified that *BRAF* mutations as well as *BRAF-KIAA1549* fusions are common in intracranial low-grade gliomas (LGGs). Fewer studies have tested for the presence of these genetic aberrations in spinal LGGs. The aim of this study was to better understand the prevalence of BRAF and other genetic aberrations in spinal LGG. METHODS: We analyzed 46 spinal LGGs from children age 1–25 years from two institutions, Children's Hospital Colorado (CHCO) and The Hospital for Sick Children (Sick Kids) for the presence of *BRAF* fusions or mutations. Data was correlated with clinical information. A 67 gene panel additionally screened for other possible genetic abnormalities of interest in the patient cohort from CHCO. In the Sick Kids cohort, $BRAF^{V600E}$ was tested for by ddPCR and IHC while BRAF fusions where detected by FISH, RT-PCR or Nanostring platform. RESULTS: Of the 31 patient samples who underwent fusion analysis, 13 (42%) harbored the *BRAF-KIAA1549* fusion. Overall survival (OS) for patients confirmed positive for *BRAF-KIAA1549* was 100% compared to 76% for fusion negative patients. Other mutations of interest were also identified in this patient cohort including *BRAFV600E, STK11*, *PTPN11*, *H3F3A*, *APC*, *TP53*, *PIK3CA* (polymorphism), *FGFR1,* and *CDKN2A* deletion. CONCLUSION: *BRAF-KIAA1549* was seen in higher frequency than *BRAFV600E* or other genetic aberrations in pediatric spinal LGGs and trends towards longer OS although not statistically significant.

LGG-35. FUNCTIONAL GENOMIC APPROACHES TO IDENTIFY THERAPEUTIC TARGETS IN *MYB* AND *MYBL1* EXPRESSING PEDIATRIC LOW-GRADE GLIOMAS

Alexandra-Larisa Condurat[1,2], Annika Wefers[3,4], Elizabeth Gonzalez[1,2], Jeyna Doshi[1], Prasidda Khadka[1,2], Selin Jessa[5,6], Jessica Tsai[1,2], Graham Buchan[1,2], Cecile Rouleau[7], Tanaz Abid[2], Amy Goodale[2], Nicole Persky[2], Rameen Beroukhim[7,2], David Root[2], Keith Ligon[8], Nada Jabado[9,10], Clauda L. Kleinman[6,9], Federica Piccioni[2], David T.W. Jones[4,11], and Pratiti Bandopadhayay[1,2]; [1]Department of Pediatric Oncology, Dana-Farber Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA, [2]Broad Institute of MIT and Harvard, Cambridge, MA, USA, [3]Department of Neuropathology, Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany, [4]Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany, [5]Quantitative Life Sciences, McGill University, Montreal, Canada, [6]Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Montreal, Canada, [7]Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, MA, USA, [8]Department of Oncologic Pathology, Dana-Farber Cancer Institute, Boston, MA, USA, [9]Department of Human Genetics, McGill University, Montreal, Canada, [10]The Research Institute of the McGill University Health Center, Montreal, Canada, [11]Pediatric Glioma Research Group, German Cancer Research Center (DKFZ), Heidelberg, Germany

AIM: Recurrent structural variants involving *MYB* and *MYBL1* transcription factors were recently identified in pediatric low-grade gliomas (pLGGs), such as the *MYB-QKI* rearrangement in Angiocentric Gliomas and truncations of *MYBL1* (*MYBL1tr*) in Diffuse Astrocytomas. However, therapeutic dependencies induced by these alterations remain unexplored. METHODOLOGY: We have generated *in vitro* pLGG mouse neural stem cell (NSCs) models engineered to harbor distinct *MYB/MYBL1* genomic alterations. We used single cell RNA sequencing approaches to determine the transcriptional profile and dissect the central regulatory networks of our *in vitro* pLGG models over time. To identify specific genetic dependencies associated with *MYB/MYBL1* mutations, we employed the Brie genome-wide mouse CRISPR lentiviral knockout pooled library, consisting of 78,637 single guide RNAs (sgRNAs) targeting 19,674 mouse genes. RESULTS: *MYB/MYBL1* expression in neural stem cells induced activation of cell-cycle related, glioma-related and senescence-related pathways that are involved in normal development, including activation of MAPK and mTOR signaling which are also activated in human pLGG samples. Genome-scale CRISPR-cas9 screens in isogenic NSCs expressing *MYB-QKI* or *MYBL1tr* identified differential genetic dependencies relative to GFP controls. These included regulators of cell-cycle progression and several modulators of the ubiquitin-proteasome degradation pathway. Analysis of RNA-sequencing data from human tumors revealed several of these dependencies identified in the cell line model to be differentially expressed in *MYB*-altered pLGG tumors relative to normal brain. CONCLUSION: Expression of *MYB* family alterations induces expression of key developmental and oncogenic pathways and genetic dependencies that represent potential therapeutic targets for *MYB* or *MYBL1* rearranged pLGGs.

LGG-36. DESMOPLASTIC INFANTILE GANGLIOGLIOMA (DIG) WITH A PPP1CB-ALK FUSION IN A 6-YEAR-OLD GIRL

William McDonald[1], Mahmoud Nagib[2], Robert Jenkins[3], Cristiane Ida[3], Kevin Halling[3], Mary Skrypek[2], and Anne Bendel[2]; [1]Abbott Northwestern, Minneapolis, MN, USA, [2]Children's Minnesota, Minneapolis, MN, USA, [3]Mayo Clinic, Rochester, MN, USA

Desmoplastic infantile astrocytoma (DIA) and desmoplastic infantile ganglioglioma (DIG) are benign glioneuronal tumors that typically occur in infants, involve the superficial cerebral cortex, and have an excellent prognosis. DIA/DIG are a distinct molecular entity based on DNA methylation profiling. BRAF600 mutations are frequently reported in DIG/DIA. A recent comprehensive genetic analysis of infantile hemispheric gliomas identified 2 unique groups: group 1 harbored alterations in the receptor tyrosine kinase (RTK) genes ALK, ROS1, NTRK, and MET and group 2 harbored alterations in the RAS/MAPK pathway. We report a case of a 6.5-year-old girl who presented with seizures and right homonymous hemianopia. MRI of her brain demonstrated a large cystic/solid left hemispheric mass with remodelling of the overlying skull, consistent with a long-standing process. She underwent a gross total resection (GTR) and pathology demonstrated a DIG with a PPP1CB-ALK gene fusion (exon 5 to exon 20) identified by RNA sequencing. She remains disease free 12 months following GTR. A literature review identified 4 reported cases of pediatric brain tumors with PPP1CB-ALK gene fusions including: a 3-month-old with a hemispheric high-grade glioma which recurred 4 years later and pathology showed mature ganglioglioma, with both tumors showing the identical PPP1CB-ALK gene fusion; a 10-month-old infant with a hemispheric low-grade glioma; an infant with a "congenital" hemispheric high-grade glioma; and a child with an astrocytoma with no further clinical data. PPP1CB-ALK gene fusion appears to be a rare oncogenic driver in gliomas of infancy, including DIG.