Neuro-Oncology
22(1), 163–165, 2020 | doi:10.1093/neuonc/noz192 | Advance Access date 15 October 2019

Letter to the Editor

Pediatric high-grade glioma resources from the Children's Brain Tumor Tissue Consortium

Pediatric high-grade gliomas (pHGGs) are a leading cause of pediatric cancer death but are genomically and spatially distinct.[1,2] In this report we describe the generation and characterization of pHGG reagents with linked genomic and longitudinal clinical data freely available to the community to accelerate pHGG research.[3]

The pHGG biospecimen collection, annotation, genomic sequencing, and cell line generation were coordinated by the Children's Brain Tumor Tissue Consortium (CBTTC) (https://cbttc.org), which is an international, collaborative, multi-institutional research program dedicated to the study of childhood brain tumors. After project proposal approval, the specimens are delivered to investigators while CBTTC data are available for viewing and download from the Gabriella Miller Kids First Data Resource Center (KF-DRC, https://kidsfirstdrc.org) or as processed data in PedcBioPortal (https://pedcbioportal.org). All subjects consented to tissue and data collection through CBTTC Institutional Review Board–approved protocols. The KF-DRC is recognized as a National Institutes of Health Trusted Partner for data sharing protections.

The CBTTC cohort of pHGG primary tumors represents the spectrum of disease. The clinical covariates, genomics, and biospecimens of the pHGG set in this study are shown in Figure 1. The cohort with tumor whole genome sequencing represents 73 participants. Tumors were from participants with a median age of 9 years at diagnosis and 55% were female. Sixty percent were from initial or diagnostic specimens and 46% were from a hemispheric location. Analysis of a selected set of recurrently mutated pHGG genes was of an expected distribution with 47% *TP53*, 36% *H3.3*, 24% *ATRX*, and 7% *BRAF* V600E variants.[2] Tumors had mutually exclusive *H3.3* G34 and K27M mutations and co-occurring mutations of *ATRX* with H3.3 G34R or *NF1*.[4,5] Seven participants' tumors demonstrated features of hypermutation with somatic and/or germline mismatch repair deficiency.[6]

At the time of study initiation, the CBTTC biorepository had 37 pHGG tumor tissues stored in freezing media that were dissociated and cultured with 4 different culturing conditions. At least one culture grew from 23/37 (62%) dissociation events from 23/73 (31%) patients in our cohort. Patient derived cell line information including prior patient therapy, culture, and growing conditions, including orthotopic xenografts, doubling times, and validation status are described elsewhere.[3] The cell line panel represents the spectrum of pHGG genomics with 8 unique patient cell lines with *H3.3* mutations (35%), 6 with *TP53* mutations (26%), 1 with a *BRAF* V600E mutation, and 1 with a *KRAS* Q61H mutation. Three patient cell lines were derived from tumors with mismatch repair deficiency and hypermutation.

For each of the tumors in the CBTTC there are additional banked biospecimens including tumor tissue, tumor in freezing media, blood, plasma, cerebrospinal fluid, and both tumor and blood derived nucleic acids (https://cbttc.org). Of the pHGG cohort in this study, 36 patient tumors are also available on a tissue microarray. This valuable resource will enable researchers to examine the tumor microenvironment, discover cell surface immunotherapy target proteins, or perform validation studies of the corresponding proteomic dataset. Finally, to facilitate integrative studies, most of the tumors in the pHGG set have corresponding redacted operative reports and pathology and radiology reports, along with the relevant MRI images and histology slides. Supplementary Figure 1 shows reagents for patient PT_9BZETMOM (7316-158 and 7316-5317), whose diagnosis and relapse tumors have the rare H3.3 G34R mutation.

In summary, the CBTTC with its member institutions, donors, patients, and families has developed an infrastructure to support pHGG research for both large genomic projects and individual laboratories. The CBTTC pHGG patient tumors and associated datasets are expected to increase, which when integrated with adult cancer and other disease sets promise to advance discoveries and hope of effective therapies for this devastating disease.

Supplementary Material

Supplementary data are available at *Neuro-Oncology* online.

Funding

This work was supported by CBTTC Foundation Partners: https://cbttc.org/partnerships/
This work is supported by the Human Tumor Atlas Network, grant U2C CA233285.

Conflict of interest statement. None.

CBTTC Member Institutions. Ann & Robert H. Lurie Children's Hospital of Chicago; Children's Hospital of Philadelphia; Children's National Health System; Seattle Children's; Stanford University/Lucile Packard Children's Hospital; University of California San Francisco Benioff Children's Hospital; UPMC Children's Hospital of

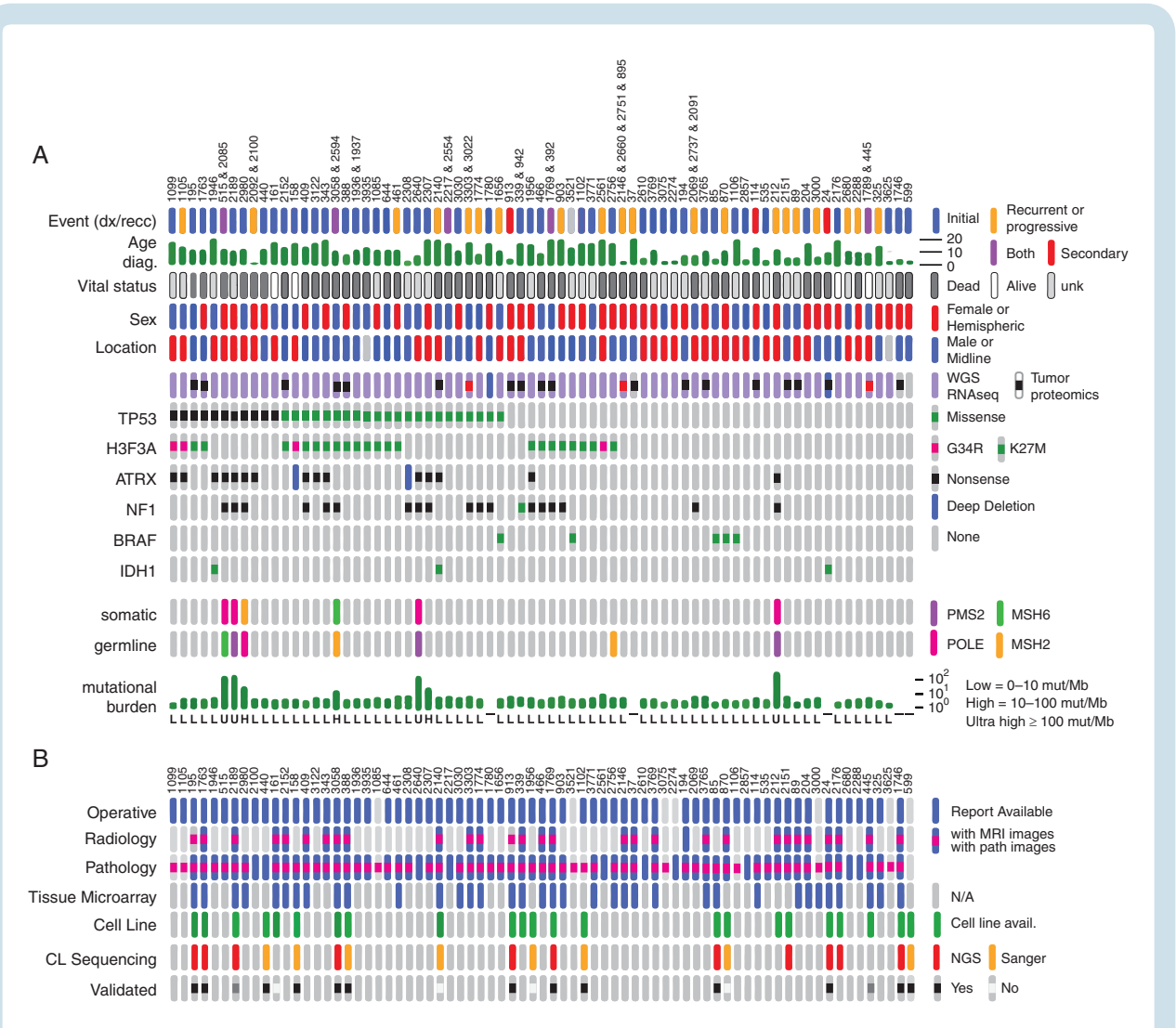

Fig. 1 The CBTTC pHGG cohort. OncoPrint of the clinical covariates, genomics, and resources of the pHGG cohort. dx = diagnosis; recc = recurrence; NGS = next generation sequencing of cell lines.

Pittsburgh; Weill Cornell Medicine Pediatric Brain and Spine Center.

Heba Ijaz,* Mateusz Koptyra,* Krutika S. Gaonkar, Jo Lynne Rokita, Valerie P. Baubet, Lamiya Tauhid, Yuankun Zhu, Miguel Brown, Gonzalo Lopez, Bo Zhang, Sharon J. Diskin, Zalman Vaksman, Children's Brain Tumor Tissue Consortium, Jennifer L. Mason, Elizabeth Appert, Jena Lilly, Rishi Lulla, Thomas De Raedt, Allison P. Heath, Alex Felmeister, Pichai Raman, Javad Nazarian, Maria Rita Santi, Phillip B. Storm, Adam Resnick, Angela J. Waanders, and Kristina A. Cole

Division of Oncology, Department of Pediatrics, Children's Hospital of Philadelphia (CHOP), Philadelphia, Pennsylvania (H.I., G.L., S.J.D., Z.V., T.D.R., K.A.C.); The Center for Data Driven Discovery in Biomedicine, CHOP, Philadelphia, Pennsylvania (M.K., J.L.R., V.P.B., L.T., Y.Z., M.B., B.Z., J.L.M., E.A., J.L., A.P.H., P.B.S., A.R., A.J.W.); The Children's Brain Tumor Tissue Consortium, Operations Center at CHOP, Philadelphia, Pennsylvania (M.K., V.P.B., L.T., J.L.M., E.A., J.L., P.B.S., A.R., A.J.W.); Department of Biomedical and Health Informatics, CHOP, Philadelphia, Pennsylvania (K.S.G., S.J.D., A.F., P.R.); Department of Neurosurgery, CHOP, Philadelphia, Pennsylvania (P.B.S., A.R.); Department of Pathology, CHOP, Philadelphia, Pennsylvania (M.R.S.); The Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania (S.J.D., T.D.R., M.R.S., P.B.S., K.A.C.); Division of Hematology/Oncology, Hasbro Children's Hospital, Department of Pediatrics, The Warren Alpert School of Brown University, Providence, Rhode Island (R.L.); Children's Research Institute, Children's National Medical Center, School of Medicine and Health Sciences, George Washington University, Washington, DC (J.N.); Division of Hematology, Oncology, and Stem Cell Transplant,

Ann & Robert H Lurie Children's Hospital of Chicago, Department of Pediatrics, Feinberg School of Medicine Northwestern University, Chicago, Illinois (A.J.W.)

Corresponding Author: Kristina A. Cole, M.D., Ph.D. Division of Oncology, Children's Hospital of Philadelphia, Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA (colek@email.chop.edu).

*Contributed equally to this work.

References

1. Jones C, Karajannis MA, Jones DTW, et al. Pediatric high-grade glioma: biologically and clinically in need of new thinking. *Neuro Oncol*. 2017;19(2):153–161.
2. Mackay A, Burford A, Carvalho D, et al. Integrated molecular meta-analysis of 1,000 pediatric high-grade and diffuse intrinsic pontine glioma. *Cancer Cell*. 2017;32(4):520–537 e525.
3. Ijaz H, Koptyra M, Gaonkar KS, et al. Pediatric high grade glioma resources from the Children's Brain Tumor Tissue Consortium (CBTTC) and Pediatric Brain Tumor Atlas (PBTA). *bioRxiv*. 2019. doi:10.1101/656587.
4. D'Angelo F, Ceccarelli M, Tala, et al. The molecular landscape of glioma in patients with neurofibromatosis 1. *Nat Med*. 2019;25(1):176–187.
5. Korshunov A, Capper D, Reuss D, et al. Histologically distinct neuroepithelial tumors with histone 3 G34 mutation are molecularly similar and comprise a single nosologic entity. *Acta Neuropathol*. 2016;131(1):137–146.
6. Campbell BB, Light N, Fabrizio D, et al. Comprehensive analysis of hypermutation in human cancer. *Cell*. 2017;171(5):1042–1056 e1010.