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Letter to the Editor

Diffuse hemispheric glioma, H3 G34-mutant: Genomic landscape of a new tumor entity and prospects for targeted therapy

"Diffuse hemispheric glioma, H3 G34-mutant" (DHG) is being included as a new CNS grade 4 tumor type in the forthcoming 5th edition of the WHO Classification of Tumors of the Central Nervous System. DHG arises within the cerebral hemispheres of teenagers and young adults and can histologically resemble anaplastic astrocytoma, glioblastoma, or CNS embryonal tumor.[1] Affected patients have a somewhat more favorable prognosis than both "Glioblastoma, IDH-wildtype" and "Diffuse midline glioma, H3 K27M-mutant," but invariably suffer from disease recurrence and mortality using current treatment regimens.[1–3] Exploration of genomically targeted therapeutic strategies is therefore needed.

DHG is molecularly defined by a recurrent glycine to arginine or valine substitution at codon 35 of the histone H3.3 gene *H3F3A*, corresponding to amino acid 34 of the mature H3.3 protein. This p.G34R/V mutation results in steric change which blocks di- and tri-methylation of lysine 36, thereby obstructing this posttranslational modification critical for glial differentiation.[4,5] Additionally, DHG frequently have co-occurring mutational inactivation of *TP53*, and deleterious mutations in the *ATRX* chromatin remodeling gene associated with alternative lengthening of telomeres.[1–3] However, the complete genomic landscape of this new tumor entity and potential targets for precision medicine therapy have yet to be fully defined.

Here we report genomic characterization of 10 DHG tumors (Figure 1), which revealed two recurrent and potentially targetable genetic perturbations: activating mutations in *PDGFRA* and diverse alterations affecting the CDK4/6-cyclin D-p16^{INK4a}-Rb cell cycle pathway. All tumors harbored *H3F3A* p.G34R mutation, along with inactivating *TP53* and *ATRX* variants. Six tumors also harbored somatic missense mutations in *PDGFRA*, and one other tumor harbored focal high-level amplification of wildtype *PDGFRA* (70% *PDGFRA* alteration frequency). Additionally, three tumors harbored homozygous deletion or truncating mutation of *CDKN2A*, one had focal high-level amplification of *CCND2*, and one other had focal high-level amplification of *CDK6* (50% cell cycle alteration frequency). This genomic analysis has revealed the possibility of targeting mutant PDGFRA and/or activated CDK4/6 using small molecule kinase inhibitors (eg, dasatinib and abemaciclib, respectively), and genomically guided clinical trials investigating these or similar agents in children and young adults with DHG may thus be warranted.

A recent landmark study by Chen et al also found a high frequency of *PDGFRA* mutations in DHG, and demonstrated that mutant *Pdgfra* potently fuels gliomagenesis in vivo in a mouse model in concert with *Atrx* and *Tp53* inactivation.[6] Through elegant functional studies, they identified that DHG arises from *GSX2*-expressing interneuron progenitor cells and that H3.3 G34R mutation stalls differentiation by epigenetic silencing of mature neuronal genes and hijacking of the active *cis*-regulatory elements of the *GSX2* gene to drive increased *PDGFRA* expression. In combination with the frequent *PDGFRA* mutations, these functional studies indicate a fundamental role for activation of PDGFRA signaling in DHG. Analysis of the specific *PDGFRA* variants from our tumor cohort (Figure 1H) and that of Chen et al reveals most mutations occur in the extracellular immunoglobulin-like domains, but also occasionally in the transmembrane domain or the autoinhibition site in the intracellular tyrosine kinase domain (p.D842 within exon 18) commonly mutated in gastrointestinal stromal tumors (GIST). While first-generation tyrosine kinase inhibitors such as imatinib effectively inhibit select mutant isoforms of *PDGFRA*, exon 18 mutations are associated with imatinib resistance. The agent avapritinib was recently approved by the FDA for the treatment of adults with advanced GIST with *PDGFRA* exon 18 mutations. Thus, selection of the tyrosine kinase inhibitor needs to be individually tailored to the specific *PDGFRA* mutation driving each patient's tumor.

In light of these findings, we recommend prospective genomic interrogation for DHG patients to inform potential personalized therapeutic approaches and enrollment in precision medicine clinical trials investigating PDGFRA and CDK4/6 inhibitors.

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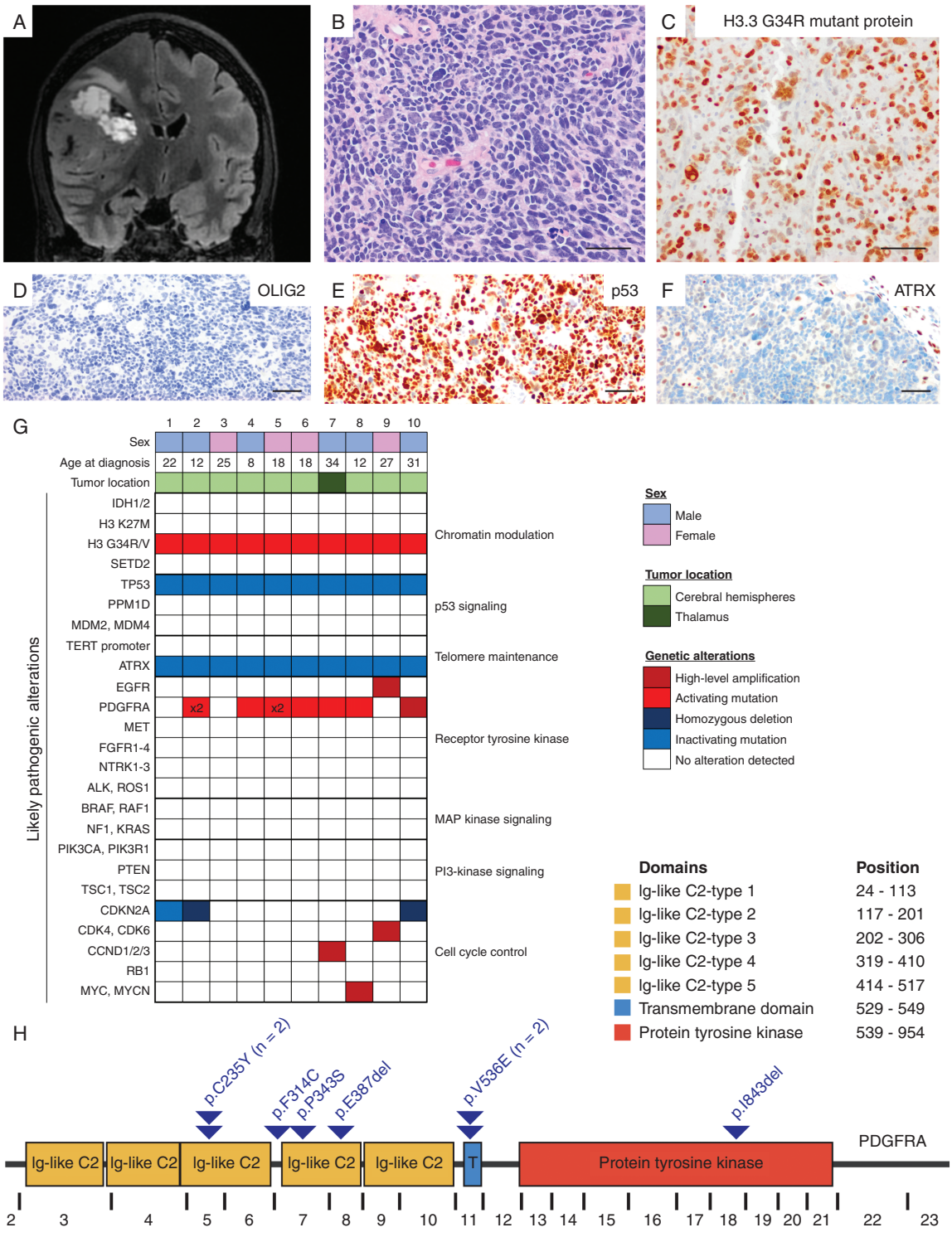

Fig. 1 Clinicopathologic features and genomic landscape of diffuse hemispheric glioma, H3 G34-mutant. (A) MR imaging typically reveals an expansile, contrast-enhancing tumor within the cerebral hemispheres. (B) Histologically these tumors are diffuse high-grade gliomas, often with a primitive embryonal-like appearance. (C) Mutant-specific antibodies have been developed to detect the H3.3 G34R or G34V-mutant protein that molecularly defines these tumors (RevMAb clones RM240 and RM307). Additional immunohistochemical findings usually include the absence of OLIG2 expression (D), p53 overexpression (E), and loss of *ATRX* expression (F). (G) Oncoprint summary table of genomic findings in a cohort of 10 DHG patients. (H) The majority of *PDGFRA* mutations localize in the extracellular immunoglobulin-like domains but may also occur within the transmembrane domain or intracellular tyrosine kinase domain (annotation per RefSeq transcript NM_006206). Scale bars, 50 μm. Abbreviations: DHG, diffuse hemispheric glioma; MR, magnetic resonance.

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Calixto-Hope G. Lucas, Sabine Mueller, Alyssa Reddy, Jennie W. Taylor, Nancy Ann Oberheim Bush, Jennifer L. Clarke, Susan M. Chang, Nalin Gupta, Mitchel S. Berger, Arie Perry, Joanna J. Phillips, and David A. Solomon

Department of Pathology, University of California, San Francisco, San Francisco, California, USA (C.-H.G.L., A.P., J.J.P., D.A.S.); Division of Pediatric Hematology/Oncology, Department of Pediatrics, University of California, San Francisco, San Francisco, California, USA (S.M., A.R.); Department of Neurology, University of California, San Francisco, San Francisco, California, USA (S.M., A.R., J.W.T., N.A.O.B., J.L.C., S.M.C.); Division of Neuro-Oncology, Department of Neurological Surgery, University of California, San Francisco, San Francisco, California, USA (J.W.T., N.A.O.B., J.L.C., S.M.C.); Department of Neurological Surgery, University of California, San Francisco, San Francisco, California, USA (S.M., N.G., M.S.B., A.P., J.J.P.); Department of Pediatrics, University of California, San Francisco, San Francisco, California, USA (N.G.)

Corresponding Author: David A. Solomon, MD, PhD, Department of Pathology, University of California, San Francisco, 513 Parnassus Avenue, Health Sciences West 451, San Francisco, CA 94143, USA (david.solomon@ucsf.edu).

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