

PubMed

Search

Display Settings: Abstract

J Clin Oncol. 2011 Oct 24. [Epub ahead of print]

Evidence for Sequenced Molecular Evolution of IDH1 Mutant Glioblastoma From a Distinct Cell of Origin.

[Lai A](#), [Kharbanda S](#), [Pope WB](#), [Tran A](#), [Solis OE](#), [Peale F](#), [Forrest WF](#), [Pujara K](#), [Carrillo JA](#), [Pandita A](#), [Ellingson BM](#), [Bowers CW](#), [Soriano RH](#), [Schmidt NO](#), [Mohan S](#), [Yong WH](#), [Seshagiri S](#), [Modrusan Z](#), [Jiang Z](#), [Aldape KD](#), [Mischel PS](#), [Liau LM](#), [Escovedo CJ](#), [Chen W](#), [Nghiemphu PL](#), [James CD](#), [Prados MD](#), [Westphal M](#), [Lamszus K](#), [Cloughesy T](#), [Phillips HS](#).

Albert Lai, Whitney B. Pope, Anh Tran, Orestes E. Solis, Jose A. Carrillo, Benjamin M. Ellingson, William H. Yong, Paul S. Mischel, Linda M. Liau, Cameron J. Escovedo, Weidong Chen, Phioanh Leia Nghiemphu, and Timothy Cloughesy, David Geffen School of Medicine at the University of California at Los Angeles, Los Angeles; Samir Kharbanda, Franklin Peale, William F. Forrest, Kanan Pujara, Ajay Pandita, Robert H. Soriano, Sankar Mohan, Somasekar Seshagiri, Zora Modrusan, Zhaoshi Jiang, and Heidi S. Phillips, Genentech, South San Francisco; C. David James, Michael D. Prados, and Heidi S. Phillips, University of California at San Francisco, San Francisco, CA; Nils O. Schmidt, Manfred Westphal, and Katrin Lamszus, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; Kenneth D. Aldape, MD Anderson Cancer Center, Houston, TX; and Chauncey W. Bowers, no affiliation.

Abstract

PURPOSE Mutation in isocitrate dehydrogenase 1 (IDH1) at R132 (IDH1(R132MUT)) is frequent in low-grade diffuse gliomas and, within glioblastoma (GBM), has been proposed as a marker for GBMs that arise by transformation from lower-grade gliomas, regardless of clinical history. To determine how GBMs arising with IDH1(R132MUT) differ from other GBMs, we undertook a comprehensive comparison of patients presenting clinically with primary GBM as a function of IDH1(R132) mutation status. **PATIENTS AND METHODS** In all, 618 treatment-naïve primary GBMs and 235 lower-grade diffuse gliomas were sequenced for IDH1(R132) and analyzed for demographic, radiographic, anatomic, histologic, genomic, epigenetic, and transcriptional characteristics. **Results** Investigation revealed a constellation of features that distinguishes IDH1(R132MUT) GBMs from other GBMs (including frontal location and lesser extent of contrast enhancement and necrosis), relates them to lower-grade IDH1(R132MUT) gliomas, and supports the concept that IDH1(R132MUT) gliomas arise from a neural precursor population that is spatially and temporally restricted in the brain. The observed patterns of DNA sequence, methylation, and copy number alterations support a model of ordered molecular evolution of IDH1(R132MUT) GBM in which the appearance of mutant IDH1 protein is an initial event, followed by production of p53 mutant protein, and finally by copy number alterations of PTEN and EGFR. **CONCLUSION** Although histologically similar, GBMs arising with and without IDH1(R132MUT) appear to represent distinct disease entities that arise from separate cell types of origin as the result of largely nonoverlapping sets of molecular events. Optimal clinical management should account for the distinction between these GBM disease subtypes.

PMID: 22025148 [PubMed - as supplied by publisher]

[+ LinkOut - more resources](#)