

News Release

Title

Prognostic relevance of genetic alterations in diffuse lower-grade gliomas

Key Points

- A larger number of broad CNVs and somatic mutations were significantly associated with poor prognosis and higher histological grade in LGGs.
- Sets of subtype-specific genetic and clinicopathological markers were delineated for each WHO subtype.
- In IDH-wildtype lower-grade gliomas (LGGs), the subsets of patients identified by these markers are likely to represent subtypes that differ in terms of overall survival, mean age, genetic profile, and patterns of DNA methylation.

Summary

This work is mainly from the team of Atsushi Natsume (Associated professor, Department of Neurosurgery) and Kosuke Aoki (Assistant professor, Department of Neurosurgery) in Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu) and Seishi Ogawa (Professor, Department of Pathology and Tumor Biology) in Graduate School of Medicine Kyoto University (Dean: Shinji Uemoto), in collaboration with Kumamoto University, Kyushu University, Oita University, and Tokyo Women's Medical University.

The clinical significance of genetic lesions within each LGG subtype has not been fully elucidated. In this study, they identified sets of subtype-specific genetic and clinicopathological markers for each WHO subtype. The study subjects were a large cohort of patients who were genotyped for known or putative driver mutations and copy number variations associated with LGGs. Importantly, given that LGGs frequently have an indolent clinical history, the subjects were followed up for sufficiently long periods to accurately evaluate overall survival. In IDH-wildtype LGGs, the subsets of patients identified by these markers are likely to represent subtypes that differ in terms of overall survival, mean age, genetic profile, and patterns of DNA methylation, suggesting that they likely represented biologically different subtypes. Their results could be used to establish a set of novel prognostic biomarkers, allowing patients within each LGG subtype to be further stratified for better clinical management.

The paper was published on the journal of *Neuro-Oncology* on July 18th, 2017.

Research Background

Diffuse lower-grade gliomas (LGGs) are genetically classified into three distinct subtypes based on IDH mutation status and co-deletion of chromosome 1p and 19q (1p/19q). However, the subtype-specific effects of additional genetic lesions on survival are largely unknown.

Research Results

A larger number of broad copy number variations (CNVs) and somatic mutations were significantly associated with poor prognosis and histological grade in LGGs, which suggest that they could be associated with more aggressive LGG phenotypes. In Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, *NOTCH1* mutations and incomplete resection were significantly associated with shorter survival. In Astrocytoma, IDH-mutant, *PIK3R1* mutations, and altered retinoblastoma pathway genes (*RBI1*, *CDKN2A*, and *CDK4*) were independent predictors of poor survival. In IDH-wildtype LGGs, co-occurrence of 7p gain, 10q loss, and mutation in the *TERT* promoter, and grade III histology independently predicted poor survival. IDH-wildtype LGGs without any of these factors were diagnosed at a younger-age, and were less likely to have genetic lesions characteristic of glioblastoma, in comparison with other IDH-wildtype LGGs, suggesting that they likely represented biologically different subtypes. These results were largely confirmed in the TCGA cohort.

Research Summary and Future Perspective

They delineated a set of subtype-specific makers that predict poor clinical outcomes in LGGs. Our results could be used to establish a set of novel prognostic biomarkers, allowing patients within each LGG subtype to be further stratified for better clinical management.

Publication

Kosuke Aoki, Hideo Nakamura, Hiromichi Suzuki, Keitaro Matsuo, Keisuke Kataoka, Teppei Shimamura, Kazuya Motomura, Fumiharu Ohka, Satoshi Shiina, Takashi Yamamoto, Yasunobu Nagata, Tetsuichi Yoshizato, Masahiro Mizoguchi, Tatsuya Abe, Yasutomo Momii, Yoshihiro Muragaki, Reiko Watanabe, Ichiro Ito, Masashi Sanada, Hironori Yajima, Naoya Morita, Ichiro Takeuchi, Satoru Miyano, Toshihiko Wakabayashi, Seishi Ogawa and Atsushi Natsume. Prognostic relevance of genetic alterations in diffuse lower-grade gliomas. *Neuro-Oncology*, July 18, 2017

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