論　文　内　容　の　要　旨
Synopsis of Thesis

氏　名 Name	梅原　徹
論文題名 Title	Distribution differences in prognostic copy number alteration profiles in IDH-wild-type glioblastoma cause survival discrepancies across cohorts （初発 IDH 野生型膠芽腫における地域間予後格差をもたらす分子遺伝学的背景）

論文内容の要旨

〔目　的(Purpose)〕

The diagnosis and prognostication of glioblastoma (GBM) remain to be solely dependent on histopathological findings and a few molecular features in IDH and MGMT, despite the clinical heterogeneity in this entity. Among diverse molecular alterations in GBM, the copy number alteration (CNA) usually shows a distinctive landscape with synchronous genomic gains and/or losses. One of the major interests with regards to the CNAs is towards the availability of prognostic and/or diagnostic stratification, but no consensus has been reached as to which CNA has a clinical value beyond the WHO grading. For achieving accurate prognostic stratification in GBM, we investigated molecular distribution of CNAs and its relationship to clinical outcome using two independent population-based IDH-wild-type GBM cohorts: an original Japanese cohort and a dataset from The Cancer Genome Atlas (TCGA). When targeting two different population from east Asia and TCGA, another concern is the geographical diversity in clinical and molecular profiles of GBMs. Therefore, the molecular disproportions between these cohorts were also dissected in light of cohort differences in GBM.

〔方法ならびに成績(Methods/Results)〕

Methods: The analyses of this retrospective study consisted of two steps (Step1 and 2). Briefly, Step1 aimed to investigate the somatic landscape including CNAs in the primary IDH wild-type GBM and compared the somatic landscapes of the two cohorts with each other. In Step2, we investigated the clinical impact of CNA profiles in further selected cases treated with radiotherapy of 50–65 Gy and concurrent temozolomide after initial surgery. The Japanese cohort was collected from cases registered in Kansai Molecular Diagnosis Network for CNS tumors (KNBTG). To assess CNAs, we used Multiplex Ligation-dependent Probe Amplification (MLPA). An extensive molecular data and clinical information in TCGA were collected from cBioPortal for Cancer Genomics and the supplemental data of the previous publication by TCGA.

Results: In Step1, the somatic landscape around CNAs was analyzed for 212 KNBTG cases and 359 TCGA cases. The major CNA, frequently observed in KNBTG, were CDKN2A deletion (62.3%), EGFR amp/gain (56.1%), and PTEN deletion (44.3%). The comparative profiling indicated unequal distribution of CNAs in these major loci among the two cohorts. Especially, the triple overlapping presence of CNAs in EGFR, CDKN2A, and PTEN (triple CNA) were much higher in frequency in TCGA (70.5%) than KNBTG (24.3%). In Step2, the clinical impacts of CNA profiles were investigated for 140 KNBTG cases and 152 TCGA cases. The KNBTG cohort significantly showed better prognosis than the TCGA cohort (median overall survival 19.3 vs 15.6 months) ($p = 0.014$, log-rank test). Thus, population from KNBTG showed longer survival than that from TCGA, regardless of postoperative radiation with concurrent temozolomide. Next, the prognostic impact of each clinical or molecular factors were examined. In univariate Cox regression analysis, triple CNA was the common unfavorable prognostic factor among two cohorts, as well as age ≥ 65 at diagnosis, MGMT unmethylation, and NFKBIA deletion. Triple CNA conclusively remained as the common prognostic factors even in a multivariate Cox model in both cohorts. Thus, the clinical significance of triple CNA was validated in two independent cohorts. All cases in Step2 ($n = 292$) were subdivided into subgroups with or without triple CNA to apply its adjustment. Remarkably, the statistical discrepancies of survival between KNBTG and TCGA completely resolved after adjusting by the triple CNA status. Accordingly, triple CNA was validated as a universal prognostic factor responsible for the survival difference between KNBTG and TCGA.

〔総　括(Conclusion)〕

We conclude that triple CNA harbors significant impacts on the survival of GBM patients, and that the distribution of CNAs potentially affects clinical outcomes across cohorts. We believe that the GBM classification according to copy number profiles would be a prognostic indicator and provide new insight into the interpretation and comparison of interregional clinical trials.

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論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

日本人を含むアジア人種の膠芽腫患者が予後良好であることが知られていたが、その背景についてはこれまで十分に明らかになっていなかった。このような膠芽腫の予後格差の背景を明らかにすべく、申請者は我が国におけるIDH野生型膠芽腫の分子遺伝学的検討と詳細な生存解析を行い、さらに米国（TCGA）のデータベースと比較検討を行った。本邦からの症例数は200例を超え、希少がんである膠芽腫においては、アジア発の膠芽腫コホートとしては過去最大級となる。本研究により、EGFR遺伝子増幅・PTEN遺伝子欠失・CDKN2A遺伝子欠失などの遺伝子コピー数異常プロファイルの組み合わせが膠芽腫患者の新たな層別化の指標となり得ることが示されただけでなく、これらの分布・頻度の違いが日本と欧米間で見られる予後格差の主たる説明因子となっていることを示唆する結果を得た。本研究成果に至る多施設共同研究を計画・主導し、筆頭著者である申請者は学位の授与に値するものと認める。