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Molecular Genetic Profile of 300 Japanese Patients with Diffuse Gliomas Using a Glioma-tailored Gene Panel

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Abstract

Rapid technological advances in molecular biology, including next-generation sequencing, have identified key genetic alterations in central nervous system (CNS) tumors. Accordingly, the fifth edition of the World Health Organization (WHO) CNS tumor classification was published in 2021. We analyzed 303 patients with diffuse glioma using an amplicon-based glioma-tailored gene panel for detecting 1p/19q codeletion and driver gene mutations such as *IDH1/2*, *TERTp*, *EGFR*, and *CDKN2A/B* on a single platform. Within glioblastomas (GBMs), the most commonly mutated genes were *TERTp*, *TP53*, *PTEN*, *NF1*, and *PDGFRA*, which was the most frequently mutated tyrosine kinase receptor in GBM, followed by *EGFR*. The genes that most commonly showed evidence of loss were *PTEN*, *CDKN2A/B*, and *RB1*, whereas the genes that most commonly showed evidence of gain/amplification were *EGFR*, *PDGFRA*, and *CDK4*. In 22 grade III oligodendroglial tumors, 3 (14%) patients had *CDKN2A/B* homozygous deletion, and 4 (18%) patients had *ARID1A* mutation. In grade III oligodendroglial tumors, an *ARID1A* mutation was associated with worse progression-free survival. Reclassification based on the WHO 2021 classification resulted in 62.5% of grade II/III *isocitrate dehydrogenase* (*IDH*)-wildtype astrocytomas being classified as *IDH*-wildtype GBM and 37.5% as not elsewhere classified. In summary, our glioma-tailored gene panel was applicable for molecular diagnosis in the WHO 2021 classification. In addition, we successfully reclassified the 303 diffuse glioma cases based on the WHO 2021 classification and clarified the genetic profile of diffuse gliomas in the Japanese population.

Keywords: gene panel, next-generation sequencing, molecular genetic profile, WHO 2021 classification

Introduction

Due to the implementation of the revised 2016 World Health Organization (WHO) classification, the diagnosis of central nervous system (CNS) tumors has changed from a histology-based approach to an integrated diagnosis that combines histology and molecular characteristics.[1)] In this integrated diagnosis, *isocitrate dehydrogenase* (*IDH*) *1* or *2* gene mutation (*IDH* mutation), codeletion of chromosomal arms 1p and 19q (1p/19q codeletion), and *H3K27M* mutation are genetic alterations that need to be evaluated.[1)] To date, it has been reported that there are biologically relevant alterations in some core pathways, namely, the p53 pathway (*MDM2*, *MDM4*, and *TP53*), the Rb pathway

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(*CDK4*, *CDK6*, *CCND2*, *CDKN2A/B*, and *RB1*), and various components influencing the PI3K pathway (*PIK3CA*, *PIK3R1*, *PTEN*, *EGFR*, *PDGFRA*, and *NF1*).[2,3] Other genetic alterations are known to play an important role in gliomas such as *TERTp*, which may serve as diagnostic, prognostic, and therapeutic biomarkers.[4,5]

Recently, WHO upgraded the classification scheme of CNS tumors. This 2021 WHO classification (5th edition) modified some important diagnostic criteria, integrating the important implications for tumor classification and patient care advocated by the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy.[6-8] Importantly, the WHO 2021 classification allows for a diagnosis of glioblastoma (GBM), which is CNS WHO grade 4, in *IDH*-wildtype astrocytomas, even in the absence of high-grade histopathologic features, when at least one of the following molecular features is present: *TERTp* mutation, *EGFR* amplification, or concurrent +7/−10.[6] Moreover, grade II or III *IDH*-mutant diffuse astrocytomas in the revised 2016 WHO classification would be diagnosed as grade 4 *IDH*-mutant astrocytomas if *CDKN2A/B* homozygous deletion is detected.[6] Given that molecular diagnosis has gained more importance in the diagnosis of glioma, molecular platform to detect key molecular alteration is urgently needed.

We recently developed an amplicon-based glioma-tailored gene panel comprising 50 genes to detect driver gene mutations, such as those in *IDH1/2*, *TERTp*, *EGFR*, and *CDKN2A/B*, and the 1p/19q codeletion based on a single platform.[9] This platform enables us to not only perform an integrated diagnosis but also detect driver gene mutation profiles in glioma.

Here, we successfully analyzed 303 cases of diffuse glioma using our glioma-tailored gene panel and revealed the molecular genetic profile in Japanese patients with diffuse gliomas and the distinct subgroups of *IDH*-wildtype GBM. In addition, we reclassified all the tumors integrated in this study according to the WHO 2021 classification and discussed the current problems of this new diagnostic scheme.

Materials and Methods

Diffuse glioma samples

Three hundred three formalin-fixed paraffin-embedded (FFPE) tumor tissue samples were collected from the Kagoshima University, Kyushu University, and University of Occupational and Environmental Health. The study was approved by the Institutional Review Board of Kagoshima University (approval no. 180104) and complied with the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients. Resected tumors were fixed with phosphate-buffered 10% formalin within 24 h of sampling and routinely processed for paraffin embedding, followed by sectioning for hematoxylin and eosin staining. All tumors were originally classified according to the WHO 2016 classification. All tissues were histologically evaluated by board-certified pathologists (M.K. and A.T.) to ensure an estimated tumor cell content of 30% or more. In all patients, when analyzing copy number variations, we sequenced the leukocyte DNA for comparison against matched tumor DNA.

DNA extraction and quantification

For the DNA preparation of the FFPE samples, we used the Maxwell 16 FFPE Tissue LEV DNA Purification kit (Promega, Madison, USA) according to the manufacturer's instructions. Thereafter, the concentration of DNA was measured using a Qubit 3.0 Fluorometer dsDNA BR Assay kit (Life Technologies, Carlsbad, USA), and DNA quality was monitored using the QIAseq DNA QuantiMIZE kit (QIAGEN, Hilden, Germany). The extracted DNA was diluted to a concentration of 5-10 ng/μL as a template, and PCR was performed using the QIAseq DNA QuantiMIZE kit. DNA with a quality check score <0.04 was considered high-quality DNA.

Next-generation sequencing

Next-generation sequencing (NGS) was performed using an amplicon-based glioma-tailored gene panel, with 2244 primers for the regions of interest (161179 bp) and an average exon coverage of 99.95%, as described previously.[9] Amplicon sequences were aligned to the human reference genome GRCh37 (hg19) in the target region of the sequence. Data were analyzed using the QIAGEN Web Portal service (https://www.qiagen.com/us/shop/genes-and-pathways/data-analysis-center-overview-page/) and Mitsubishi Space Software (Amagasaki, Hyogo, Japan, https://www.mss.co.jp/business/life-science/).

Data analysis

We used OncoPrinter (cbioportal.org/oncoprinter) and MutationMapper (cbioportal.org/mutation_mapper), which are tools in the cBioPortal for Cancer Genomics, to visualize and analyze our data.[10,11] Cluster analysis was performed based on the Euclidean distance with the vegan package and Ward. D2 linkage with the ComplexHeatmap package. This analysis was performed using R open-source statistical computing language (v3.5.3) and the integrated development environment RStudio (v0.99.484) as well as the R packages nmf (v0.20.6), mass (v7.3-51.5), and stats (v 3.2.2). Statistical analysis was performed with GraphPad Prism software (version 9.2.0). A difference was considered statistically significant at $p < 0.05$.

Results

Genetic features of diffuse gliomas

Among the 185 GBM cases, the average age of the patients was 63.5 years. *IDH1* mutation was detected in 7 out

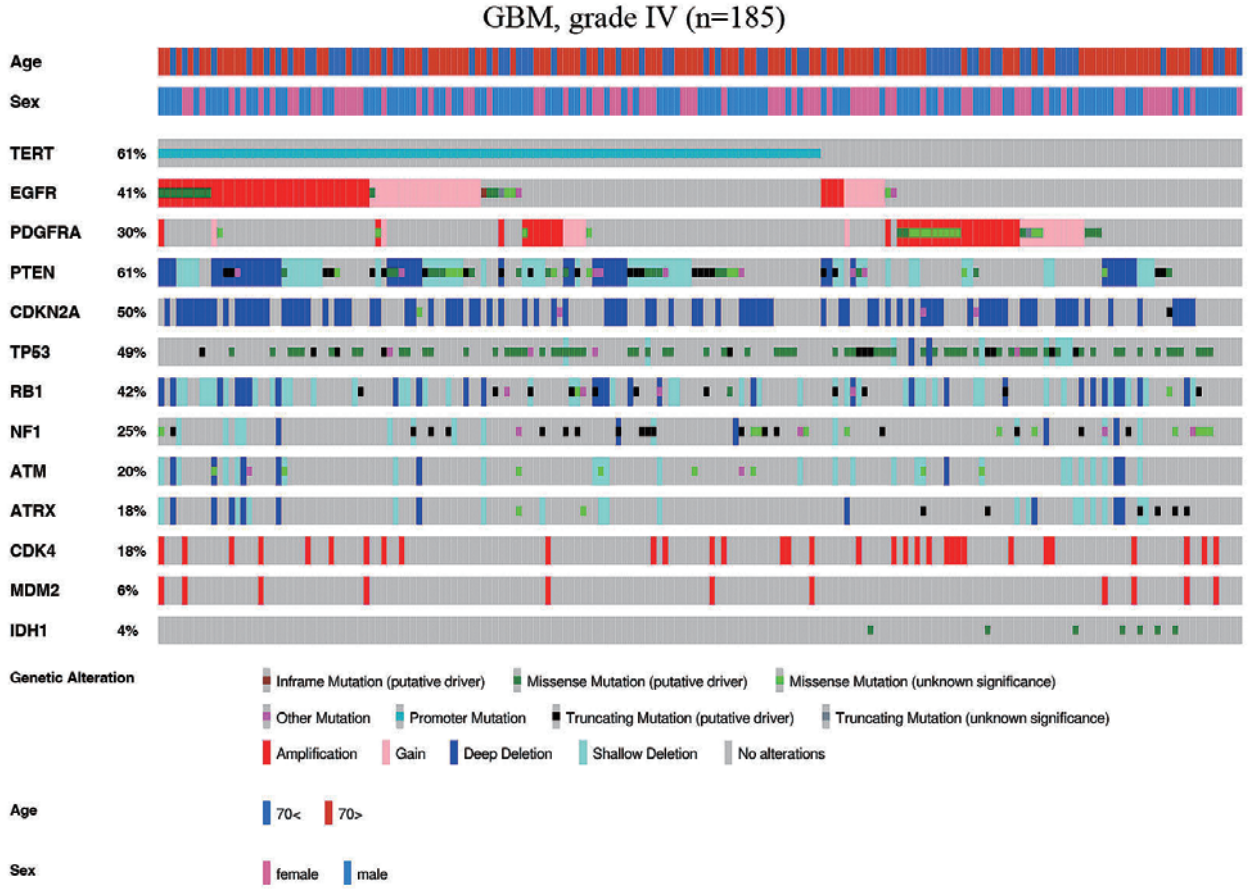

Fig. 1 Somatic alterations of driver genes in glioblastoma. Driver gene mutations and copy number alterations were generated and visualized using OncoPrinter, which is included in the cBioPortal for Cancer Genomics software suite.

of 185 cases (4%) (Fig. 1). No mutations and copy number alterations were detected in 4 (2.2%) cases of GBMs. The most commonly mutated genes were *TERTp* (61%), *TP53* (46%), *PTEN* (31%), and *NF1* (18%) (Fig. 2A), and *PDGFRA* (12%) was the most frequently mutated tyrosine kinase receptor in GBM, followed by *EGFR* (10%) (Fig. 1). The genes that most commonly showed evidence of a hemizygous or homozygous deletion were *PTEN* (48%), *CDKN2A/B* (48%), and *RB1* (37%), whereas the most common genes showing evidence of gain/amplification were *EGFR* (gain, 14%; amplification, 22%), *PDGFRA* (gain, 10%; amplification, 17%), and *CDK4* (amplification, 18%) (Fig. 2A). The representative mutual exclusivity was observed in the pairs of *PDGFRA* and *TERTp* ($p < 0.001$), *PDGFRA* and *EGFR* ($p < 0.001$), and *CDKN2A* and *CDK4* ($p < 0.001$). The representative co-occurrence was observed in the pairs of *ATM* and *RB1* ($p < 0.001$), *ATM* and *ATRX* ($p < 0.001$), *CDK4* and *MDM2* ($p < 0.001$), *TERTp* and *PTEN* ($p < 0.001$), and *TERT* and *EGFR* ($p < 0.001$). Patient clinical information and molecular status are listed in Supplementary Table S1.

Among 31 diffuse astrocytoma (DA) cases, the average age of the patients was 47.5 years. The most commonly mutated genes were *TP53* (68%), *IDH1* (65%), and *ATRX* (26%) (Fig. 2B). The average age of patients with DA carrying *IDH1* mutations was 40.3 years, whereas that of patients with DA without mutations averaged 60.5 years ($p = 0.008$). The genes that most commonly showed evidence of a hemizygous or homozygous deletion were *PTEN* (26%), *RB1* (19%), and *ATRX* (10%) (Fig. 2B). There were no cases of *IDH*-mutant DA with *CDKN2A/B* homozygous deletion (Fig. 3A). *TERTp* mutation was detected in 5 out of 31 cases (16%) (Fig. 3A). One patient had *EGFR* amplification, and one had *EGFR* gain/*PTEN* loss, which was the surrogated marker of the combined whole chromosome 7 gain and whole chromosome 10 loss, both associated with *TERTp* mutations (Fig. 3A). DA lacking *IDH1* and *TERTp* mutations showed TP53 mutations, *PTEN* hemizygous or homozygous deletions, and *RB1* hemizygous or homozygous deletions (Fig. 3A). Patient clinical information and molecular status are listed in Supplementary Table S2.

Among 33 anaplastic astrocytoma (AA) cases, the average age of the patients was 50.7 years. The most commonly mutated genes were *TP53* (48%), *TERTp* (42%), and *ATRX* (39%) (Fig. 2C). The incidence of *TERTp* and *EGFR* mutations in AA was higher than that in DA (Fig. 3A, B). The genes that most commonly showed evidence of a

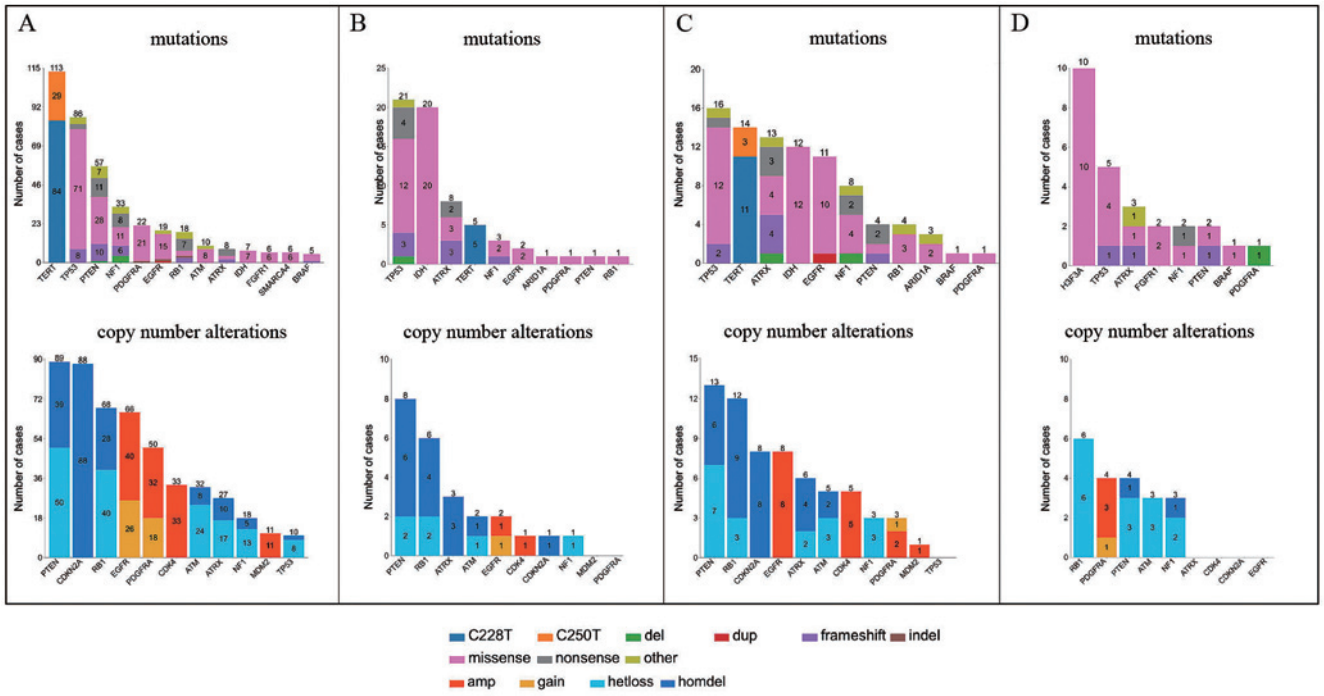

Fig. 2 Frequency of gene mutations (upper) and copy number alterations (lower) of glioblastoma (A), diffuse astrocytoma (B), anaplastic astrocytoma (C), and diffuse midline glioma (D).

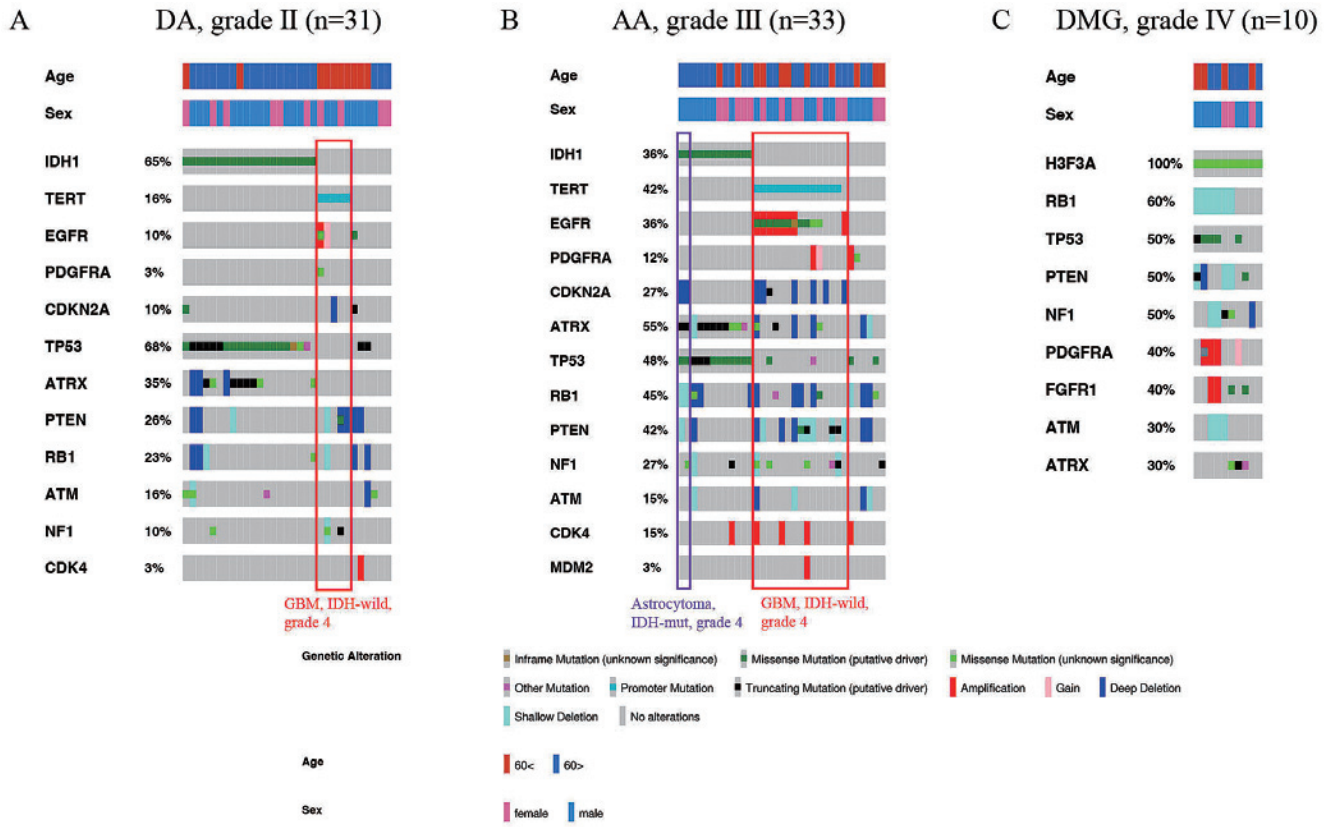

Fig. 3 Somatic alterations of driver genes in diffuse astrocytoma (A), anaplastic astrocytoma (B), and diffuse midline glioma (C). Driver gene mutations and copy number alterations were generated and visualized using OncoPrinter, which is included in the cBioPortal for Cancer Genomics software suite.

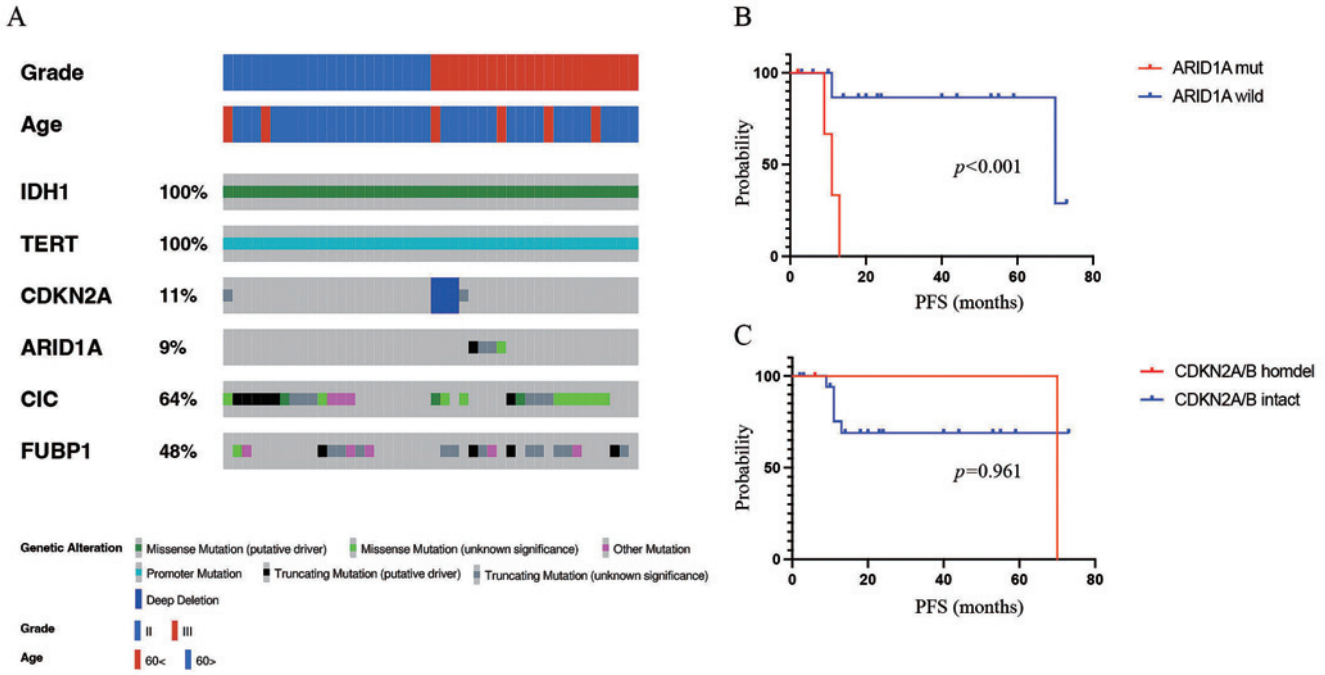

Fig. 4 Somatic alterations of driver genes in oligodendroglial tumors. (A) Driver gene mutations and copy number alterations were generated and visualized using OncoPrinter, which is included in the cBioPortal for Cancer Genomics software suite. (B) Kaplan–Meier analysis of progression-free survival (PFS) of patients with grade III oligodendroglial tumors with and without *ARID1A* mutations. (C) Kaplan–Meier analysis of PFS of patients with grade III oligodendroglial tumors with and without *CDKN2A/B* homozygous deletions.

hemizygous or homozygous deletion were *PTEN* (39%), *RB1* (36%), and *CDKN2A/B* (24%), whereas the genes that most commonly showed evidence of amplification were *EGFR* (24%) and *CDK4* (15%) (Fig. 2C). *IDH1* mutation was detected in 12 out of 33 cases (36%) (Fig. 3B). The average age of patients with AA carrying *IDH1* mutations was 40.6 years, whereas that of patients with AA without mutations averaged 56.5 years (p = 0.003). In *IDH*-mutant AA, two cases showed *CDKN2A/B* homozygous deletion (Fig. 3B). *TERTp* mutation was detected in 14 out of 33 cases (42%), *EGFR* amplification was detected in 8 out of 33 cases (24%), and *EGFR* gain/*PTEN* loss was not detected (Fig. 3 B). The mutual exclusivity was observed in the pairs of *IDH1* mutation and *TERTp* mutation. AA lacking *IDH1* and *TERTp* mutations and *EGFR* amplification showed *PDGFRA* alterations and a lack of *CDKN2A/B* homozygous deletion (Fig. 3B). Patient clinical information and molecular status are listed in Supplementary Table S3.

Among 10 diffuse midline glioma (DMG) cases, the average age of the patients was 47.5 years. The most commonly mutated genes were *H3F3A* (100%), *TP53* (50%), and *ATRX* (30%), whereas no *TERTp* mutations and *EGFR* alterations were detected (Fig. 2D). The genes that most commonly showed evidence of a hemizygous or homozygous deletion were *RB1* (60%), *PTEN* (40%), *ATM* (30%), and *NF1* (30%), whereas the gene that most commonly showed evidence of gain/amplification was *PDGFRA* (gain, 10%; amplification, 30%) (Fig. 2D). The incidence of *PDGFRA* and *FGFR1* alterations in DMG was higher than that in other astrocytic tumors (Fig. 3C).

Among 44 oligodendroglial tumor cases (grade II, 22 cases; grade III, 22 cases), the average age of the patients was 47.4 years. All patients had *IDH1* mutations, 1p/19q codeletion, and *TERTp* mutations, and *CIC* was frequently mutated in oligodendroglial tumor, followed by *FUBP1* (Fig. 4A). In 22 grade III oligodendroglial tumors, 3 (14%) patients had *CDKN2A/B* homozygous deletion, and 4 (18%) patients had *ARID1A* mutation (Fig. 4A). In 22 grade III oligodendroglial tumors, an *ARID1A* mutation was associated with worse progression-free survival (PFS) (Fig. 4B), whereas a *CDKN2A/B* homozygous deletion was not associated with PFS (Fig. 4C). Patient clinical information and molecular status are listed in Supplementary Table S4.

Mutation distributions of *EGFR* and *PDGFRA* in diffuse gliomas

Nineteen GBM cases, 11 AA cases, and 2 DA cases had *EGFR* mutations, and the frequency of *EGFR* mutations in AA (33%) was higher those that in GBM (10%) and DA (6%) (Fig. 3A-C). Five cases had two *EGFR* point mutations, and one case had three *EGFR* point mutations. We also identified mutations in the *EGFR* kinase domain in 19% of the sites (7/36 mutation sites) (Supplementary Table S5). $EGFR^{A289D/T/V}$ was the most common missense mutation, fol-

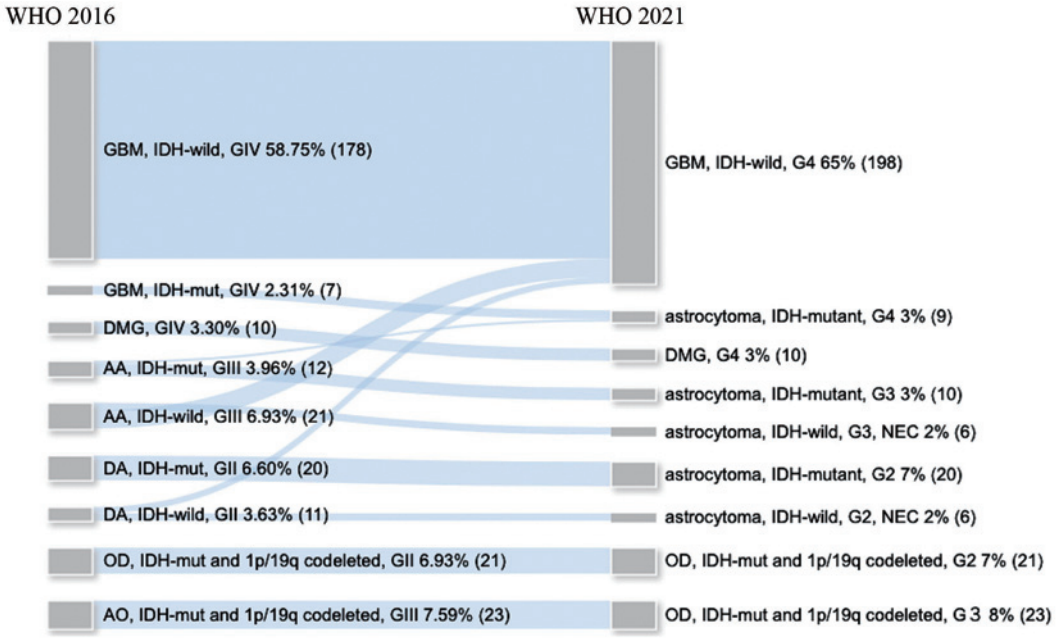

Fig. 5 Results of the molecular reclassification of 303 diffuse gliomas from the retrospective cohort according to the World Health Organization (WHO) 2021 classification. The diagram shows the diagnostic change between the diagnosis based on the WHO 2016 classification (left) and the diagnosis based on the WHO 2021 classification (right).

lowed by *EGFR*^{R108K} (Supplementary Table S5). On the other hand, 22 GBM cases, 1 AA case, 1 DA case, and 1 DMG case had *PDGFRA* mutations, and the frequency of *PDGFRA* mutations in GBM (12%) was higher than those in other astrocytic tumors (Fig. 2). Five cases had two *PDGFRA* point mutations, and one case had three *PDGFRA* point mutations. We also identified mutations in the *PDGFRA* kinase domain in 23% of the sites (7/31 mutation sites) (Supplementary Table S6). *PDGFRA*^{N468S} was the most common missense mutation (Supplementary Table S6).

Reclassification of the retrospective cohort based on the WHO 2021 classification

The analysis of the NGS data resulted in successful reclassification of all 303 diffuse gliomas according to the WHO 2021 classification. The reclassification resulted in a marked increase in the number of patients with *IDH*-wildtype GBMs (from 178 to 198 patients) (Fig. 5). No changes in patient numbers after reclassification were seen for WHO grade II and III oligodendroglial tumors and WHO grade IV DMGs (Fig. 5). Among the seven *IDH*-mutant GBMs, all cases were classified as *IDH*-mutant astrocytoma of WHO grade 4 (Fig. 5). Moreover, among the *IDH*-wildtype DA, 5 (45%) were classified into *IDH*-wildtype GBM, WHO grade 4, and 6 (55%) were classified into the not elsewhere classified (NEC) category (Fig. 5). Among the *IDH*-wildtype AAs, 15 (71%) were classified into *IDH*-wildtype GBM, WHO grade 4, and 6 (29%) were classified into the NEC category (Fig. 5). Among DAs and AAs, both PFS and overall survival (OS) were stratified by grade based on the WHO 2016 classification (Fig. 6A, B), whereas for the WHO 2021 classification, both PFS and OS were stratified more precisely by grade (Fig. 6C, D).

Unsupervised hierarchical cluster analysis of *IDH*-wildtype GBM, grade 4

We next performed an unsupervised hierarchical cluster analysis of the 198 *IDH*-wildtype GBMs classified according to the WHO 2021 classification. This analysis revealed three major distinct groups of *IDH*-wildtype GBMs. One major cluster (Cluster A) was characterized by mutations in *TERTp* and *EGFR*, the amplification of *EGFR*, the homozygous deletion of *CDKN2A/B*, the hemizygous or homozygous deletion of *PTEN*, and a lack of *TP53* mutations (Fig. 7A). A second major cluster (Cluster B) was classified by mutations in *TERTp*, *PTEN*, and *TP53*, as well as a lack of *CDKN2A/B* homozygous deletions (Fig. 7A). The third major cluster (Cluster C) was characterized by mutations in *TP53* and *PDGFRA*, the amplification of *PDGFRA*, the homozygous deletion of *CDKN2A/B*, and a lack of *TERTp* and *PTEN* mutations (Fig. 7A). The OS was significantly shorter for Cluster C than for Clusters A and B (p = 0.035; Fig. 7B).

Discussion

Here, we revealed the molecular genetic profile in Japanese patients with diffuse gliomas and two major distinct groups of *IDH*-wildtype GBMs using a glioma-tailored gene panel. Moreover, we successfully reclassified the diffuse

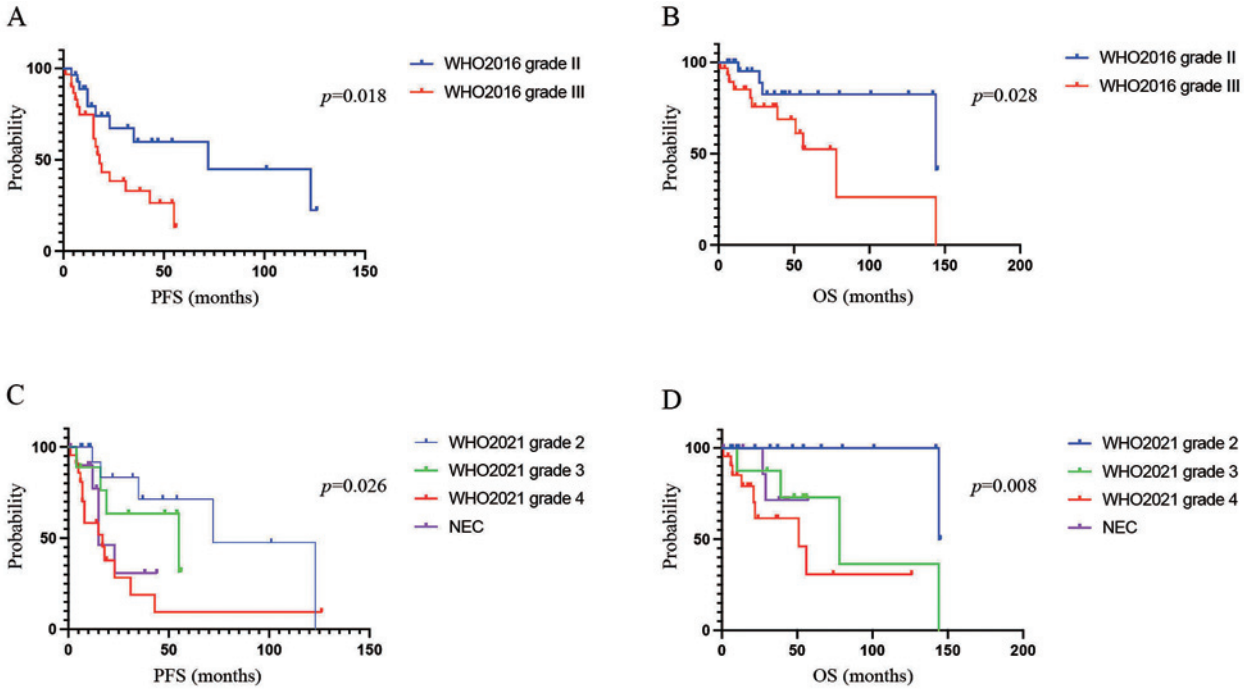

Fig. 6 Kaplan–Meier analysis of progression-free survival (PFS) and overall survival (OS) according to the World Health Organization (WHO) 2016 and 2021 classification based on patients with grade II and III astrocytic tumors. (A) Kaplan–Meier analysis of PFS according to the WHO 2016 classification for patients with grade II and III astrocytic tumors. (B) Kaplan–Meier analysis of OS according to the WHO 2016 classification for patients with grade II and III astrocytic tumors. (C) Kaplan–Meier analysis of PFS according to the WHO 2021 classification for patients with grade II and III astrocytic tumors. (D) Kaplan–Meier analysis of OS according to the WHO 2021 classification for patients with grade II and III astrocytic tumors.

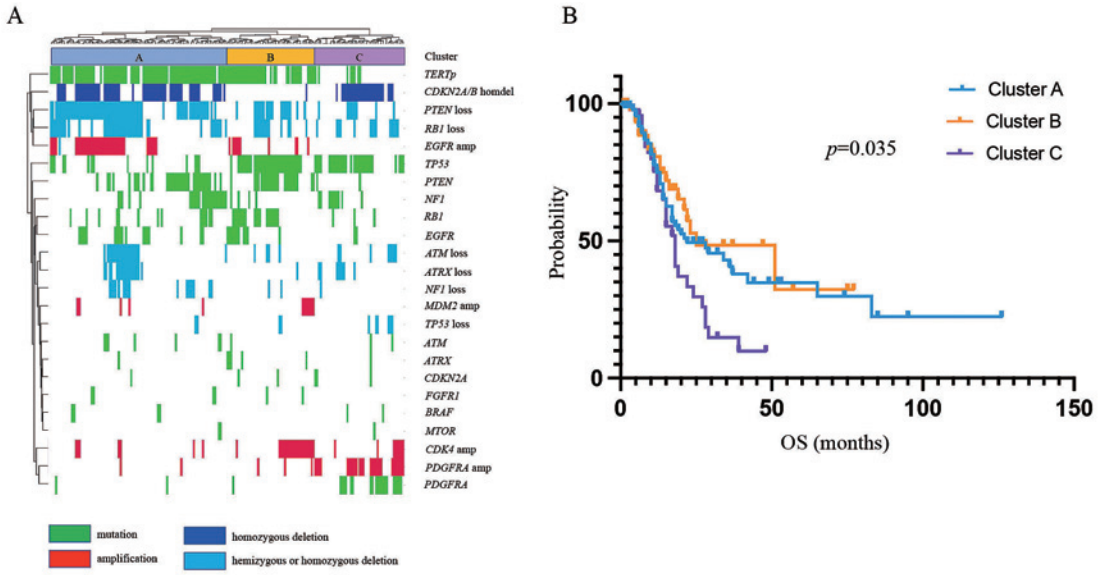

Fig. 7 Unsupervised hierarchical clustering analysis. (A) Results of the unsupervised hierarchical clustering analysis of the 198 *IDH*-wildtype glioblastomas based on the World Health Organization (WHO) 2021 classification. (B) Survival analysis comparing Clusters A, B, and C by unsupervised hierarchical clustering analysis of the 198 *IDH*-wildtype glioblastomas.

gliomas according to the WHO 2021 classification.

One of the incorporated markers for the classification of diffuse gliomas is the *TERT* promoter mutation. Recent reports have indicated that 70%-80% of GBM genomes harbor *TERTp* mutations.[12-14] On the contrary, lower frequencies were reported in the Japanese groups that were stud-

ied.[5,15-17] In our cohort, 61% of GBM showed mutations in *TERTp*, suggesting that *TERTp* mutations may be less frequent in Japan than in other countries. The reason for this discrepancy in the frequency of *TERTp* mutation remains unknown. Another notable finding was that 22% of GBMs showed *EGFR* amplification. Lower *EGFR* amplification rates in patients with GBM from Asia were recently reported during a screening for the INTELLANCE1 and INTELLANCE2 randomized GBM trials as compared to that in other regions.[18] Moreover, lower frequencies of *EGFR* amplifications were reported in the Japanese groups as compared to that in other populations, which was compatible with our results.[16,17,19] Previous studies have reported a co-expression association between *TERTp* mutations and *EGFR* amplification,[16,17] and the reason why the frequency of both *TERTp* and *EGFR* amplification is lower in the Japanese group than in other countries may be due to racial differences. Moreover, in our study, $EGFR^{A289D/T/V}$ was the most common missense mutation, which was comparable with the results of a previous study.[2] A previous report indicated increased tumor invasion associated with $EGFR^{A289D/T/V}$ and revealed a significant reduction in the OS of patients with tumors harboring this variant, making it a potential therapeutic target.[20]

In addition, we collected more samples than that in our previous study,[9] and using hierarchical molecular classification of *IDH*-wildtype GBM, we revealed three distinct major groups. Notably, Cluster C was characterized by mutations in *PDGFRA*, the amplification of *PDGFRA*, and a lack of *TERTp* mutations and *EGFR* alterations. The OS was significantly shorter for Cluster C than for Clusters A and B, which was similar to the findings of our previous study.[9] *TERTp* and *EGFR* are important markers for molecular diagnosis in the WHO 2021 classification and have been reported to be associated with prognosis.[4,6,21] In addition, our results suggested that *PDGFRA* is an important driver gene in the molecular classification of GBM. *PDGFRA* mutations were associated with high proliferative activity via the platelet-derived growth factor receptor α and the cyclin-dependent kinase (CDK) 4/CDK6-cyclin D1 signaling pathways in a ligand-independent manner.[22] In particular, $PDGFRA^{N468S}$ confers high sensitivity to multikinase inhibitors, receptor tyrosine kinase inhibitors, and CDK4/CDK6 inhibitors, making it a potential therapeutic target.[22] Moreover, compared with that in grade II astrocytomas, grade III astrocytomas had a higher burden of molecular alterations, including *TERTp* mutation, *EGFR* alterations, and *CDKN2A/B* homozygous deletion.

In our study, 14% had *CDKN2A/B* homozygous deletion in grade III oligodendroglial tumors but not in grade II oligodendroglial tumors. Some studies revealed that the presence of *CDKN2A/B* homozygous deletion was a strong adverse prognostic factor for PFS and OS in grade III oligodendroglial tumors.[23,24] Some studies did not observe any *CDKN2A/B* homozygous deletion in grade II oligodendroglial tumor, which was compatible with our results,[23] whereas other studies reported *CDKN2A/B* homozygous deletion in some cases of grade II oligodendroglial tumors.[25,26] In addition, 18% had *ARID1A* mutation in grade III oligodendroglial tumors but not in grade II oligodendroglial tumors. In grade III oligodendroglial tumors, an *ARID1A* mutation was associated with worse PFS. *ARID1A* functions as a tumor suppressor, wherein the majority of mutations are nonsense or frame-shift, resulting in a loss of protein expression.[27] *ARID1A* mutations were more frequent in oligodendroglial tumors than in astrocytic tumors. Although there is one report of *ARID1A* mutations in oligodendrogliomas,[28] to the best of our knowledge, our study is the first to demonstrate that *ARID1A* mutations are associated with worse PFS. The *ARID1A* mutation may be involved in the malignant transformation of oligodendroglial tumors, as it was found only in grade III oligodendrogliomas and not in grade II oligodendroglial tumors.

With the implementation of the WHO 2021 classification, molecular genetic information is an increasingly crucial component of the standard diagnostic work-up of diffuse gliomas.[6] Our study found *IDH* mutations in 65% of patients with DA and 36% of patients with AA, both having a lower frequency of *IDH* mutations than that in previous reports.[29] Based on the WHO 2021 classification, in grade II/III *IDH*-wildtype astrocytomas, 62.5% were classified into *IDH*-wildtype GBM, and 37.5% were classified into the NEC category. Fujimoto et al. reported that *PDGFRA* gain/amplification has a poor prognosis in *IDH*-wildtype *TERTp*-wildtype lower grade gliomas, which corresponds to the NEC category in the WHO 2021 classification.[30] Therefore, *PDGFRA* gain/amplification is likely to serve as an additional marker to molecularly define GBM in the NEC category. However, a significant number of grade II/III *IDH*-wildtype astrocytomas were found to be classified into the NEC category, and further molecular classification of the NEC category is needed.

In summary, our glioma-tailored gene panel of 50 genes was applicable for molecular diagnosis, in accordance with the WHO 2021 classification. In addition, in the reclassification of 303 diffuse glioma cases based on the WHO 2021 classification, we revealed the molecular genetic profile of Japanese patients with diffuse gliomas.

Supplementary Material

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Conflicts of Interest Disclosure

The authors declare that they have no competing interests.

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