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Differences in methylation profiles between long-term survivors and short-term survivors of IDH-wild-type glioblastoma

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Abstract

Background. Patients with glioblastoma (GBM) have a median overall survival (OS) of approximately 16 months. However, approximately 5% of patients survive >5 years. This study examines the differences in methylation profiles between long-term survivors (>5 years, LTS) and short-term survivors (<1 year, STS) with isocitrate dehydrogenase (IDH)-wild-type GBMs.

Methods. In a multicenter retrospective analysis, we identified 25 LTS with a histologically confirmed GBM. They were age- and sex-matched to an STS. The methylation profiles of all 50 samples were analyzed with EPIC 850k, classified according to the DKFZ methylation classifier, and the methylation profiles of LTS versus STS were compared. **Results**. After methylation profiling, 16/25 LTS and 23/25 STS were confirmed to be IDH-wild-type GBMs, all with +7/–10 signature. LTS had significantly increased O6-methylguanine methyltransferase (MGMT) promoter methylation and higher prevalence of FGFR3-TACC3 fusion (P = .03). STS were more likely to exhibit CDKN2A/B loss (P = .01) and higher frequency of NF1 (P = .02) mutation. There were no significant CpGs identified between LTS versus STS at an adjusted *P*-value of .05. Unadjusted analyses identified key pathways involved in both LTS and STS. The most common pathways were the Hippo signaling pathway and the Wnt pathway in LTS, and GPCR ligand binding and cell–cell signaling in STS. **Conclusions**. A small group of patients with IDH-wild-type GBM survive more than 5 years. While there are few differences in the global methylation profiles of LTS compared to STS, our study highlights potential pathways involved in GBMs with a good or poor prognosis.

Key Points

- A small subset of patients with an isocitrate dehydrogenase wild-type glioblastoma survive >5 years.
- While the global methylation patterns between short-term and long-term survivors are similar, our study highlights genes and pathways that can explain these survival differences.

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Importance of the Study

Glioblastoma (GBM) is the most common primary malignant brain tumor in adults. The vast majority have a very poor prognosis. A small population of isocitrate dehydrogenase (IDH)-wild-type GBMs are long-term survivors (LTS), defined as >3 years in previous studies. Genetically, GBMs are very heterogeneous. Since methylation has become a very accurate tool in the diagnosis and classification of central nervous system tumors, we studied the methylation profiles of LTS, defined in this study as >5 years, compared to short-term

Glioblastomas (GBMs) are the most common primary malignant brain tumors in adults.¹ The median overall survival (OS) of patients with a GBM is approximately 16 months.^{2–5} A small population of glioblastoma patients survive for more than 5 years after their initial diagnosis. They are considered longterm survivors (LTS) and make up about 5% of GBM patients.^{6,7}

Several clinical factors, such as younger age at diagnosis, high-performance status, maximal tumor resection, and treatment with radiation and chemotherapy, are associated with better outcomes in patients with GBM.⁸⁻¹⁰

Over the last decades, molecular features have become more important in understanding the pathology of glioma. Isocitrate dehydrogenase (IDH) mutation has been associated with long-term survival (>36 months),¹¹ and a group of alterations has been associated with a worse prognosis: epidermal growth factor receptor (EGFR) amplification, gain of chromosome 7 and loss of chromosome 10 (+7/-10), and telomerase reverse transcriptase promotor (TERTp) mutations. These findings have been incorporated in the 2021 World Health Organization (WHO CNS5) classification: an IDH-wild-type(wt) diffuse glioma with 1 or more of these alterations defines a GBM regardless of histological grade.¹² Moreover, the WHO CNS5 is the first CNS classification that included methylation profiling, which can be done using the DKFZ classifier, and is highly accurate in diagnosing and subtyping CNS tumors.¹³To date, some molecular features within IDHwt glioma in adult patients (ie, GBM) seem to have a prognostic role, including O6-methylguanine methyltransferase (MGMT), cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B), and TERT.^{14–16}

Among these prognostic molecular makers in IDH-wildtype GBM, MGMT promoter methylation is the most well established. MGMT is a gene that encodes a DNA repair protein responsible for removing alkyl groups from guanine residues. Epigenetic silencing by promoter methylation has been associated with improved survival in patients with GBM treated with alkylated agents such as temozolomide and lomustine in trials.^{17,18} Furthermore, in large cohort studies, MGMT hypermethylation was associated with better survival^{7,19}

In previous studies, LTS was defined as surviving more than 3 years after initial diagnosis.^{20–23} Those studies that defined LTS as surviving more than 5 years included IDH-mutant GBMs in their cohort,^{24,25} and as discussed above, being IDH-wild-type is the hallmark of a GBM.

survivors (STS; <1 year). We showed that methylation is very useful in identifying true IDH-wild-type GBM, since some LTS had a mismatch in their methylation classification diagnosis compared to their histological diagnosis and were another entity. Moreover, methylation analysis identified differences in key genes between LTS and STS, and different activated pathways in LTS, compared to STS. This analysis leads to a better understanding of what characterizes a favorable or poor prognosis in IDH-wild-type GBM.

While next-generation sequencing and methylation analysis have given us a greater understanding of molecular features that may lead to a better survival in GBMs, we still do not have a complete understanding of why certain GBM patients survive significantly longer than others. The identification of a precise gene signature has been challenging given the genetic heterogeneity of GBM and the limited number of patients with long-term survival. The purpose of this study was to characterize the methylation profile of GBMs in patients with long-term survival (defined as an OS of >5 years) compared to short-term survivors (STS; defined as <1 year). We used methylation profiling to select "true" IDH-wild-type GBM, excluding other diagnoses that can mimic a GBM histologically (eg, pleomorphic xantroastrocytoma [PXA] and astrocytoma, IDH mutant, WHO grade 4). In addition, following methylation analysis, we aimed to determine which pathways were upregulated in long-term and short-term GBM survivors.

Methods

Patients

We selected adult (≥18 years old) patients with a histologically confirmed GBM, diagnosed between January 1995 and December 2010. Patients were diagnosed at St. Michael's Hospital or at University Health Network, Toronto, Ontario, Canada. Radiation and chemotherapy treatment were given at Princess Margaret Cancer Centre, Toronto, Ontario, Canada. Those who survived >5 years after surgery were matched, based on sex and age (±3 years) at the time of diagnosis, to GBM patients who survived <1 year. Patients were excluded if samples for methylation profiling were unavailable and/or if follow-up data were missing. All samples were obtained during the first surgical procedure. For all patients, age at diagnosis, sex, tumor location, extent of resection, primary treatment, and survival were collected.

Methylation Profiling

DNA from tumor samples was extracted from formalinfixed paraffin-embedded (FFPE) tissue (QIAamp DNA

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FFPE Tissue Kit, Qiagen). Subsequently, between 200 and 550 ng of DNA was then bisulfite converted (EZ DNA methylation Kit, Zymo Research) and hybridized on the Infinium MethylationEPIC BeadChip array (Illumina, San Diego, CA).²⁶ The methylation results were classified according to the DKFZ methylation classifier, v11b4 (https:// www.molecularneuropathology.org/mnp/).¹³ The methylation classifier provides a list of methylation classes and calibrated methylation scores between 0 and 1 for each methylation class, with a higher score representing a higher confidence in the associated methylation class. Each of the 3 GBM subtypes (classical, mesenchymal, and proneural) has a distinct methylation class and calibrated methylation score. Only tumors identified as IDHwild-type GBM in all 3 of the top methylation classifier results, independent of GBM subtype, were included for further analyses. All tumors identified as non-GBM methylation classes in the top 3 methylation classifier results were removed, regardless of calibrated score. In this manner, heterogeneous primary IDH-wild-type GBM

were still included, but samples that may not be GBM k were removed. r Tumor Purity r

The leukocyte unmethylation for purity (LUMP) score was calculated for all samples with DNA methylation data, as previously described, to estimate tumor purity/cellularity.²⁷ In short, the LUMP score is calculated by taking the average methylation levels of 44 CpG sites, which have been shown to be unmethylated in immune cells and methylated in tumors in a pan-cancer analysis, and dividing the number by 0.85. LUMP estimates were compared between prognostic subtypes.

samples with low calibrated scores for 1 specific subtype

MGMT Status

MGMT methylation status was obtained directly from the DKFZ classifier v11b4 reports, which uses the MGMT-STP27 algorithm and validated cutoff as previously described by Bady et al.²⁸

CNV Analyses

Methylation data were analyzed for copy-number variations using the *conumee* package in R by comparing the 29 CNS-relevant genes used by default in the DKFZ methylation classifier²⁹ between the long-term and short-term survival groups.

Methylation Data Processing

Raw methylation data within.idat files were processed in R v4.0.3 (R Foundation for Statistical Computing) using the *minfi* package and data was normalized using the single-sample Noob approach. CpG sites with low-quality data for 1 or more samples (CpG detection P > .01) were removed from further analysis as well as those located on

X and Y chromosomes, overlapping with single-nucleotide polymorphisms, or designated as cross-reactive.

Differential CpG Analysis

Differential CpG analysis was performed on LTS versus STS samples. At an unadjusted level, statistically significant *P*-values were defined as those with P < .05 and delta Beta (dB) of 0.1 or greater. The number of differentially methylated CpGs (hypermethylated and hypomethylated) after correction for multiple testing was measured using a range of adjusted *P*-values and dB values.

Pathway Analysis

All CpGs from the above differential analysis were mapped to areas of the genome and only CpGs within the gene promoter region were selected for analysis. In this manner, genes with promoter hypomethylation were considered to be upregulated, and genes with promoter hypermethylation were considered to be downregulated.³⁰ While previous research has suggested that gene promoter methylation is associated with gene expression,³⁰ it is important to note that not all differentially methylated genes may correspond to significant changes in gene expression.

The G:Profiler package in R was used for functional enrichment analysis, using the hypermethylated genes in LTS vs STS (downregulated in LTS and conversely upregulated in STS) and hypomethylated genes (upregulated in LTS and conversely downregulated in STS). The end results included biological processes and pathway bar plots generated.

Statistical Analysis

Differences between the LTS and STS regarding baseline characteristics, MGMT status, LUMP score, GBM subtype, and gene CNV were tested using a chi-square test for categorical data and a Mann–Whitney *U* for continuous data, respectively.

Ethics Statement

This study was approved by the Institutional Review Board (IRB) of University Health Network, University of Toronto, Ontario, Canada. The IRB waived the requirement for written informed consent for this retrospective observational study.

Results

Patients

From all patients treated for a histologically proven GBM in Princess Margaret Cancer Centre between 1995 and 2010, 36 patients survived >5 years. Of these patients, only 25 had adequate FFPE tumor samples available for analysis. These 25 patients had a median age of 53 at diagnosis

Table 1. Baseline characteristics							
	LTS, n = 25	STS, n = 25					
Sex (<i>n</i> female)	15	14					
Age (median, IQR)	53 years, 46–56	52 years, 46–55					
Tumor location (<i>n</i>) Frontal Parietal Temporal Occipital Unknown	6 2 15 1 1	8 5 7 2 3					
Extent of resection (n) Biopsy Subtotal resection Gross total resection Unknown	1 19 5	3 19 2 1					
Primary treatment (n) Radiation Temozolomide	25 24	22 22					
Vital status	8 alive 17 dead	25 dead					
Overall survival (me- dian, IQR)	6.8 years, 5.8–9.3	0.9 years, 0.6–1.0					
IOR = interquartile range:	IOR = interquartile range: LTS = long-term survivors; n = number of						

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IQR = interquartile range; LTS = long-term survivors; *n* = number of patients; STS = short-term survivors.

(interquartile range 46–56 years old), and 15 (60%) were women. The median OS in this LTS group was 6.8 years. These patients were sex and age (\pm 3 years) matched to STS. No differences were found regarding the extent of resection and primary treatment between the LTS and STS groups (Table 1).

Methylation Profile

Methylation profiling yielded results in all 50 cases, with no samples failing due to low tumor cell content or returning a result of "no match" on the methylation classifier. Overall, 16 of the 25 LTS and 23 of 25 STS were classified as an IDH-wild-type GBM (Table 2). Nine out of the 25 LTS were classified with an alternative diagnosis, with the Heidelberg classifier: polymorphous low-grade neuroepithelial tumor of the young (n = 2), high-grade astrocytoma, IDH mutant (n = 3), PXA (n = 2), high-grade astrocytoma with piloid features (n = 1), and inflammatory environment (n = 1). In the STS, only 2 out of the 25 patients were not classified as an IDH-wild-type GBM: 1 was classified as a PXA, and the other as control tissue from the cerebral hemisphere. Only those with samples classified as glioblastoma, IDH-wild-type were included for further analysis.

Tumor Purity

There was no difference in tumor purity (LUMP score) between LTS and STS, and no differences in purity between GBM subtypes. Although there were no significant differences in GBM subtype between LTS and STS, there was a trend in increased proneural subtype in STS (Table 3).

MGMT Status and CNV Analyses

The MGMT promoter was methylated in 13 of the 16 LTS (81%), compared to 8 of the 23 STS (35%), P = .01 (Table 3). All included GBMs had a complete gain of chromosome 7 and a complete loss of chromosome 10 (+7/–10). Interestingly, LTS had a significantly higher frequency of fibroblast growth factor receptor–transforming acidic coiled-coil (FGFR3-TACC3) fusions (P = .03), compared to STS. In STS, CDKN2A/B homozygous deletion was significantly more often present (P = .01). A higher prevalence of Neurofibromin 1 (NF1) mutation was found in STS (P = .01), compared to LTS.

Methylation Data Processing and Differential CpG Analysis

All samples passed quality control assessment (sample detection P < .05). At an unadjusted level, this resulted in a total of 5863 hypermethylated CpGs and 2240 hypomethylated CpGs between LTS versus STS samples (Supplementary Table 1). However, after correction for multiple testing, there were no significantly differentiated CpGs between LTS and STS, even at a less-stringent adjusted *P*-value of \leq .2.

Pathway Analysis

Following the CpG analysis, we included 1514 hypermethylated CpGs and 559 hypomethylated CpGs, corresponding to a total of 1210 hypermethylated genes and 437 hypomethylated genes in LTS, compared to STS, from the unadjusted analysis in Supplementary Table 1. These genes are involved in several pathways. Using the Kyoto Encyclopedia of Genes and Genomes, we identified multiple upregulated pathways (Figure 1A and 1C) and biological processes (Figure 1B and 1D) in LTS (Figure 1A and 1B) and STS (Figure 1C and 1D). The Hippo pathway was the most upregulated pathway in LTS and the G-protein-coupled receptors (GPCR) pathway was the most common in STS.

Discussion

In this multicenter retrospective case–control study, we showed that a small group of IDH-wild-type GBM patients survived >5 years. Compared to STS (<1 year), there are a few differences in the global methylation profiles. We identified that LTS were more likely to have MGMT methylation and were enriched for Hippo and Wnt-signaling pathways. STS were more likely to demonstrate homozygous deletion of CDKN2A/B, NF1, and were enriched for cell–cell signaling and GPCR-related pathways.

Most other studies,^{20–22} but not all,^{9,23} also showed a significant increase in MGMT methylation in LTS. However, in contrast to our study, these studies defined LTS as a survival of >36 months, or in some cases, just >24 months. Of note, studies that did not find an increase of MGMT in LTS were smaller studies (both n = 16).

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8 LTS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, RTK1 subtype Yes 9 ILTS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 11 ITS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 12 ITS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 12 ITS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 14 ITS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 15 ITS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 15 ITS ALDH_HG MC Adult-type diffuse high-grade glioma, IDH-wild-type, subtype & (novel) Yes 16 ITS padHGG_A MC Clibustoma, IDH mutant; high-grade No 17 ITS INFLAME_ENV MC High-grade satrocytoma with piloid features No 115 INFLAME_ENV MC Polymorphous low-grade neuroepithelial tumor of the young No 12 TS FNA MC Polymorphous low-grade neuroepithelial tumor of the young N	6	LTS	GBM_MES_TYP	MC Glioblastoma, IDH-wild-type, mesenchymal subtype	Yes				
9 LTS GBM_RTK1 MC Glioblastoma, IDH-wild-type, RTK1 subtype Yes 10 LTS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 11 LTS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 12 LTS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 13 LTS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 14 LTS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 15 LTS HGG_E MC Adult-type diffuse high-grade glioma, H3 wild-type and IDH-wild-type, subtype A (novel) Yes 16 LTS A.IDH,HG MC Astrocytoma, IDH mutant; high-grade No 17 FA_A_IDH,HG MC Astrocytoma, IDH mutant; high-grade No 115 N.IFLAM_ENV MC High-grade storcytoma with piloid factures No 121 TS PLNTY MC Polymorphous low-grade neuroepithelial tumor of the young No 121 TS PXA MC Pleomorphic santhoastrocytoma No 125	7	LTS	GBM_MES_TYP	MC Glioblastoma, IDH-wild-type, mesenchymal subtype	Yes				
10 LTS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 11 LTS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 13 LTS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 14 LTS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 15 LTS HGG E MC Adult-type diffuse high-grade glioma, IDH-wild-type, subtype E (novel) Yes 16 LTS pedHGG_A MC Adult-type diffuse high-grade glioma, IDH-wild-type, subtype E (novel) Yes 17 LTS A_IDH_HG MC Astrocytoma, IDH mutant: high-grade No 18 LTS A_IDH_HG MC Astrocytoma, IDH mutant: high-grade No 10 LTS HGAP MC Inflammatory microevironment No 21 LTS INFLAM_ENV MC Inflammatory microevironment No 23 LTS PLNTY MC Polymorphous low-grade neuroepithelial tumor of the young No 24 LTS PXA MC Pleomorphic santhoastrocytoma No 25 LTS PXA MC Pleomorphic santhoastrocytoma No 26 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 27	8	LTS	GBM_MES_TYP	MC Glioblastoma, IDH-wild-type, mesenchymal subtype	Yes				
11 LTS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 12 LTS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 14 LTS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 15 LTS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 15 LTS HGG_E MC Adult-type diffus high-grade glioma, ID wild-type and IDH-wild-type, subtype A (novel) Yes 16 ITS pedHGG_A MC Astrocytoma, IDH mutant: high-grade No 17 LTS A, IDH_HG MC Astrocytoma, IDH mutant: high-grade No 18 ITS A, IDH, MG MC Astrocytoma, IDH mutant: high-grade No 11 ITS N, IDH, AM MC Astrocytoma, IDH mutant: high-grade No 12 ITS PLNTY MC Peloymorphous low-grade neuroepithelial tumor of the young No 12 ITS PLNTY MC Pelomorphic santhoastrocytoma No 14 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesendrymal subtype Yes 15 SGM_MES_TYP MC Glioblastoma, IDH-wild-type, mesendrymal subtype Yes 15 SGM_MES_TYP MC Glioblastoma, IDH-wild-type, mesendrymal subtype Yes	9	LTS	GBM_RTK1	MC Glioblastoma, IDH-wild-type, RTK1 subtype	Yes				
12 LTS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 13 LTS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 15 LTS HGG_E MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 16 LTS pedHGG_A MC Adult-type diffuse high-grade glioma, IDH-wild-type, and IDH-wild-type, subtype A (novel) Yes 17 LTS A_IDH_HG MC Astrocytoma, IDH mutant; high-grade No 18 ITS A_IDH_HG MC Astrocytoma, IDH mutant; high-grade No 19 LTS A_IDH_HG MC Astrocytoma, IDH mutant; high-grade No 12 ITS HGAP MC High-grade satrocytoma with piloid features No 12 ITS INFLAM_ENV MC Infimmatory microevironment No 13 ITS PLNTY MC Polymorphous low-grade neuroepithelial tumor of the young No 15 FSA MC M Colioblastoma, IDH-wild-type, mesenchymal subtype Yes 15 FSA GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes	10	LTS	GBM_RTK2	MC Glioblastoma, IDH-wild-type, RTK2 subtype	Yes				
13 LTS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 14 LTS GBM_RTK2 MC Glioblastoma, IDH-wild-type, RTK2 subtype Yes 16 LTS padHGG_A MC Diffuse padiatric-type high-grade glioma, IDH-wild-type, subtype and IDH-wild-type, subtype A (novel) Yes 17 LTS A_IDH_HG MC Astrocytoma, IDH mutant; high-grade No 18 LTS A_IDH_HG MC Astrocytoma, IDH mutant; high-grade No 20 LTS HGAP MC Astrocytoma, IDH mutant; high-grade No 21 LTS IAIPL_HG MC Astrocytoma, IDH mutant; high-grade No 22 ITS PLNTY MC Pidip-grade astrocytoma enucroepithelial tumor of the young No 23 LTS PLNTY MC Polymorphous low-grade neuroepithelial tumor of the young No 24 LTS PXA MC Pleomorphic xanthoastrocytoma No 25 LTS PXA MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 26 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 25 SGBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 25 SGBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype	11	LTS	GBM_RTK2	MC Glioblastoma, IDH-wild-type, RTK2 subtype	Yes				
14LTSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes15LTSHGG_EMC Adult-type diffuse priade glioma, IDH-wild-type, subtype E (novel)Yes16LTSA_IDH_HGMC Astrocytoma, IDH mutant; high-gradeNo18LTSA_IDH_HGMC Astrocytoma, IDH mutant; high-gradeNo19LTSA_IDH_HGMC Astrocytoma, IDH mutant; high-gradeNo10LTSA_IDH_HGMC Astrocytoma, IDH mutant; high-gradeNo21LTSIAGAPMC High-grade astrocytoma with piloid featuresNo21LTSPLNTYMC Cholymorphous low-grade neuroepithelial tumor of the youngNo21LTSPLNTYMC Cholymorphous low-grade neuroepithelial tumor of the youngNo24LTSPXAMC CPleomorphic xanthoastrocytomaNo25STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes26STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes27STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes28STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes29STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes21STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes21STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes21STS <t< td=""><td>12</td><td>LTS</td><td>GBM_RTK2</td><td>MC Glioblastoma, IDH-wild-type, RTK2 subtype</td><td>Yes</td></t<>	12	LTS	GBM_RTK2	MC Glioblastoma, IDH-wild-type, RTK2 subtype	Yes				
15 LTS HGG_E MC Adult-type diffuse high-grade glioma, IDH-wild-type, subtype E (novel) Yes 16 LTS pedHGG_A MC Diffuse pediatric-type high-grade glioma, H3 wild-type and IDH-wild-type, subtype A (novel) Yes 17 LTS A_IDH_HG MC Astrocytoma, IDH mutant; high-grade No 18 LTS A_IDH_HG MC Astrocytoma, IDH mutant; high-grade No 20 LTS HGAP MC Inflammatory microcytonma with piloid features No 21 LTS INFLAM_ENV MC Inflammatory microcytonmant No 21 LTS PLNTY MC Polymorphous low-grade neuroepithelial tumor of the young No 23 LTS PLNTY MC Polymorphous low-grade neuroepithelial tumor of the young No 24 LTS PXA MC Clioblastoma, IDH-wild-type, mesenchymal subtype Yes 25 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 25 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 26 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 25	13	LTS	GBM_RTK2	MC Glioblastoma, IDH-wild-type, RTK2 subtype	Yes				
16 LTS pedHGG_A MC Diffuse pediatric-type high-grade glioma, H3 wild-type and IDH-wild-type, subtype A (novel) Yes 17 LTS A_IDH_HG MC Astrocytoma, IDH mutant; high-grade No 18 LTS A_IDH_HG MC Astrocytoma, IDH mutant; high-grade No 19 LTS A_IDH_HG MC Astrocytoma, IDH mutant; high-grade No 20 LTS HGAP MC High-grade astrocytoma with piloid features No 21 LTS PLNTY MC Polymorphous low-grade neuroepithelial tumor of the young No 21 LTS PLNTY MC Polymorphous low-grade neuroepithelial tumor of the young No 23 LTS PLNTY MC Polymorphous low-grade neuroepithelial tumor of the young No 24 LTS PXA MC Pleomorphic xanthoastrocytoma No 25 TS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 25 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 25 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 25 STS <	14	LTS	GBM_RTK2	MC Glioblastoma, IDH-wild-type, RTK2 subtype	Yes				
17 LTS A_IDH_HG MC Astrocytoma, IDH mutant; high-grade No 18 LTS A_IDH_HG MC Astrocytoma, IDH mutant; high-grade No 19 LTS A_IDH_HG MC Astrocytoma, IDH mutant; high-grade No 20 LTS HGAP MC High-grade astrocytoma with piloid features No 21 LTS INFLAM_ENV MC Inflammatory microevironment No 21 LTS PLNTY MC Polymorphous low-grade neuroepithelial tumor of the young No 23 LTS PLNTY MC Ploomorphic xanthoastrocytoma No 24 LTS PXA MC Pleomorphic xanthoastrocytoma No 25 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 27 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 26 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 27 STG GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 27 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, RTK1 subtype Y	15	LTS	HGG_E	MC Adult-type diffuse high-grade glioma, IDH-wild-type, subtype E (novel)	Yes				
18 LTS A_IDH_HG MC Astrocytoma, IDH mutant; high-grade No 19 LTS A IDH_HG MC Astrocytoma, IDH mutant; high-grade No 20 LTS HGAP MC High-grade astrocytom with piloid features No 21 LTS INFLAM_ENV MC Inflammatory microevironment No 22 LTS PLNTY MC Polymorphous low-grade neuroepithelial tumor of the young No 23 LTS PLNTY MC Polymorphous low-grade neuroepithelial tumor of the young No 24 LTS PXA MC Pleomorphic xanthoastrocytoma No 25 LTS PXA MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 27 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 28 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 30 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 31 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 32 STS GBM_MES_TYP MC Glioblastoma, IDH-wild	16	LTS	pedHGG_A	MC Diffuse pediatric-type high-grade glioma, H3 wild-type and IDH-wild-type, subtype A (novel)	Yes				
19 LTS A_IDH_HG MC Astrocytoma, IDH mutant; high-grade No 20 LTS HGAP MC High-grade astrocytoma with piloid features No 21 LTS INFLAM_ENV MC Inflammatory microevironment No 21 LTS PLNTY MC Polymorphous low-grade neuroepithelial tumor of the young No 23 LTS PLNTY MC Polymorphous low-grade neuroepithelial tumor of the young No 24 LTS PXA MC Pelomorphic xanthoastrocytoma No 25 LTS PXA MC Pelomorphic xanthoastrocytoma No 26 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 28 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 29 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 31 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, Resenchymal subtype Yes 32 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, RTK1 subtype Yes 33 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, RT	17	LTS	A_IDH_HG	MC Astrocytoma, IDH mutant; high-grade	No				
20LTSHGAPMC High-grade astrocytoma with piloid featuresNo21LTSINFLAM_ENVMC Inflammatory microevironmentNo22LTSPLNTYMC Polymorphous low-grade neuroepithelial tumor of the youngNo23LTSPLNTYMC Polymorphous low-grade neuroepithelial tumor of the youngNo24LTSPXAMC Pleomorphic xanthoastrocytomaNo25LTSPXAMC Pleomorphic xanthoastrocytomaNo26STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes27STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes28STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes29STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes31STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes32STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes33STSGBM_RES_TYPMC Glioblastoma, IDH-wild-type, RTK1 subtypeYes34STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes35STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes35STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes35STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes35STSGBM_RTK1MC Glioblastoma,	18	LTS	A_IDH_HG	MC Astrocytoma, IDH mutant; high-grade	No				
21 LTS INFLAM_ENV MC Inflammatory microevironment No 22 LTS PLNTY MC Polymorphous low-grade neuroepithelial tumor of the young No 23 LTS PLNTY MC Polymorphous low-grade neuroepithelial tumor of the young No 24 LTS PXA MC Pleomorphic xanthoastrocytoma No 24 LTS PXA MC Pleomorphic xanthoastrocytoma No 25 TS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 27 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 26 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 27 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 27 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, mesenchymal subtype Yes 31 STS GBM_MES_TYP MC Glioblastoma, IDH-wild-type, RTK1 subtype Yes 33 STS GBM_RTK1 MC Glioblastoma, IDH-wild-type, RTK1 subtype Yes 35 STS GBM_RTK1 MC Glioblastoma, I	19	LTS	A_IDH_HG	MC Astrocytoma, IDH mutant; high-grade	No				
22LTSPLNTYMC Polymorphous low-grade neuroepithelial tumor of the youngNo23LTSPLNTYMC Pleomorphic xanthoastrocytomaNo24LTSPXAMC Pleomorphic xanthoastrocytomaNo25LTSPXAMC Pleomorphic xanthoastrocytomaNo26STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes27STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes28STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes29STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes30STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes31STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes32STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes33STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes34STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes35STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes36STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes37STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes38STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes39STSGBM_RTK1MC Glioblastoma, IDH-w	20	LTS	HGAP	MC High-grade astrocytoma with piloid features	No				
23LTSPLNTYMC Polymorphous low-grade neuropithelial tumor of the youngNo24LTSPXAMC Pleomorphic xanthoastrocytomaNo25LTSPXAMC Pleomorphic xanthoastrocytomaNo26LTSPXAMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes27STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes28STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes29STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes30STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes31STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes32STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes33STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes34STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes35STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes35STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes35STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes36STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes37STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes36STSGBM_RTK1MC Gl	21	LTS	INFLAM_ENV	MC Inflammatory microevironment	No				
24LTSPXAMC Pleomorphic xanthoastrocytomaNo25LTSPXAMC Pleomorphic xanthoastrocytomaNo26STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes27STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes28STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes29STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes31STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes32STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes33STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes34STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes35STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes34STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes35STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes36STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes37STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes38STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes39STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes40STSGBM_RTK1MC Gliob	22	LTS	PLNTY	MC Polymorphous low-grade neuroepithelial tumor of the young	No				
25LTSPXAMC Pleomorphic xanthoastrocytomaNo26STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes27STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes28STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes29STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes30STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes31STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes32STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes33STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes34STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes35STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes36STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes37STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes38STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes39STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes40STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes41STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes43STSGBM_RTK	23	LTS	PLNTY	MC Polymorphous low-grade neuroepithelial tumor of the young	No				
26STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes27STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes28STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes29STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes30STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes31STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes33STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes34STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes35STSGBM_RTK1MC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes34STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes35STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes36STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes37STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes38STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes39STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes41STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes42STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes43 <td>24</td> <td>LTS</td> <td>PXA</td> <td>MC Pleomorphic xanthoastrocytoma</td> <td>No</td>	24	LTS	PXA	MC Pleomorphic xanthoastrocytoma	No				
27STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes28STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes29STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes30STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes31STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes32STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes33STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes34STSGBM_RTK1MC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes35STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes36STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes37STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes38STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes39STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes40STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes41STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes42STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes43STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes44STS<	25	LTS	PXA	MC Pleomorphic xanthoastrocytoma	No				
22STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes29STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes30STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes31STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes32STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes33STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes34STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes35STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes36STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes38STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes39STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes39STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes40STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes41STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes42STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes43STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes44STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2<	26	STS	GBM_MES_TYP	MC Glioblastoma, IDH-wild-type, mesenchymal subtype	Yes				
29STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes30STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes31STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes32STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes33STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes34STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes35STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes36STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes37STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes38STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes39STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes40STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes41STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes42STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes44STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes44STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC	27	STS	GBM_MES_TYP	MC Glioblastoma, IDH-wild-type, mesenchymal subtype	Yes				
30STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes31STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes32STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes33STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes34STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes35STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes36STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes37STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes38STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes39STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes40STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes41STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes42STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes43STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes44STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblast	28	STS	GBM_MES_TYP	MC Glioblastoma, IDH-wild-type, mesenchymal subtype	Yes				
31STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes32STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes33STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes34STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes35STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes36STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes37STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes38STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes39STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes40STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes41STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes42STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes43STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes44STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes46STSGBM_RTK2MC Glioblastoma, IDH-w	29	STS	GBM_MES_TYP	MC Glioblastoma, IDH-wild-type, mesenchymal subtype	Yes				
32STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes33STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes34STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes35STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes36STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes37STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes38STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes39STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes40STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes41STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes42STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes43STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes44STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes46STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes46STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes47STSpedHGG_RTK1AMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass A (novel)Yes48STSpedHGG_RTK1C	30	STS	GBM_MES_TYP	MC Glioblastoma, IDH-wild-type, mesenchymal subtype	Yes				
33STSGBM_MES_TYPMC Glioblastoma, IDH-wild-type, mesenchymal subtypeYes34STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes35STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes36STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes37STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes38STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes39STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes40STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes41STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes42STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes43STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes44STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes44STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes46STSGBM_RTK4MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes46STSGBM_RTK4MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes47STSpedHGG_RTK1AMC Glioblastoma, IDH-wild-type, RTK2 subtypeYes48STSpedHGG_RTK1AMC Glioblastoma, IDH-wild-type, RT	31	STS	GBM_MES_TYP	MC Glioblastoma, IDH-wild-type, mesenchymal subtype	Yes				
34STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes35STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes36STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes37STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes38STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes39STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes40STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes41STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes42STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes43STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes44STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes46STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes47STSpedHGG_RTK1AMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass A (novel)Yes48STSpedHGG_RTK1AMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass C (novel)Yes49STS <td>32</td> <td>STS</td> <td>GBM_MES_TYP</td> <td>MC Glioblastoma, IDH-wild-type, mesenchymal subtype</td> <td>Yes</td>	32	STS	GBM_MES_TYP	MC Glioblastoma, IDH-wild-type, mesenchymal subtype	Yes				
35STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes36STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes37STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes38STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes39STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes40STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes41STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes42STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes43STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes44STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes46STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes47STSpedHGG_RTK1AMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass A (novel)Yes48STSpedHGG_RTK1CMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass C (novel)Yes49STSCTRL_HEMIMC Control tissue, cerebral hemisphereNo	33	STS	GBM_MES_TYP	MC Glioblastoma, IDH-wild-type, mesenchymal subtype	Yes				
36STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes37STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes38STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes39STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes40STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes41STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes42STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes43STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes44STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes46STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes47STSpedHGG_RTK1AMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass A (novel)Yes48STSpedHGG_RTK1CMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass C (novel)Yes49STSCTRL_HEMIMC Control tissue, cerebral hemisphereNo	34	STS	GBM_RTK1	MC Glioblastoma, IDH-wild-type, RTK1 subtype	Yes				
37STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes38STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes39STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes40STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes41STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes42STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes43STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes44STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes46STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes47STSpedHGG_RTK1AMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass A (novel)Yes48STSpedHGG_RTK1CMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass C (novel)Yes49STSCTRL_HEMIMC Control tissue, cerebral hemisphereNo	35	STS	GBM_RTK1	MC Glioblastoma, IDH-wild-type, RTK1 subtype	Yes				
38STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes39STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes40STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes41STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes42STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes43STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes44STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes46STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes47STSpedHGG_RTK1AMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass A (novel)Yes48STSpedHGG_RTK1CMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass C (novel)Yes49STSCTRL_HEMIMC Control tissue, cerebral hemisphereNo	36	STS	GBM_RTK1	MC Glioblastoma, IDH-wild-type, RTK1 subtype	Yes				
39STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes40STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes41STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes42STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes43STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes44STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes46STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes47STSpedHGG_RTK1AMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass A (novel)Yes48STSpedHGG_RTK1CMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass C (novel)Yes49STSCTRL_HEMIMC Control tissue, cerebral hemisphereNo	37	STS	GBM_RTK1	MC Glioblastoma, IDH-wild-type, RTK1 subtype	Yes				
40STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes41STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes42STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes43STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes44STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes46STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes47STSpedHGG_RTK1AMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass A (novel)Yes48STSpedHGG_RTK1CMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass C (novel)Yes49STSCTRL_HEMIMC Control tissue, cerebral hemisphereNo	38	STS	GBM_RTK1	MC Glioblastoma, IDH-wild-type, RTK1 subtype	Yes				
41STSGBM_RTK1MC Glioblastoma, IDH-wild-type, RTK1 subtypeYes42STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes43STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes44STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes46STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes47STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes47STSpedHGG_RTK1AMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass A (novel)Yes48STSpedHGG_RTK1CMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass C (novel)Yes49STSCTRL_HEMIMC Control tissue, cerebral hemisphereNo	39	STS	GBM_RTK1	MC Glioblastoma, IDH-wild-type, RTK1 subtype	Yes				
42STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes43STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes44STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes46STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes47STSgBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes48STSpedHGG_RTK1AMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass A (novel)Yes49STSCTRL_HEMIMC Control tissue, cerebral hemisphereNo	40	STS	GBM_RTK1	MC Glioblastoma, IDH-wild-type, RTK1 subtype	Yes				
43STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes44STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes46STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes47STSpedHGG_RTK1AMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass A (novel)Yes48STSpedHGG_RTK1CMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass C (novel)Yes49STSCTRL_HEMIMC Control tissue, cerebral hemisphereNo	41	STS	GBM_RTK1	MC Glioblastoma, IDH-wild-type, RTK1 subtype	Yes				
44 STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes45 STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes46 STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes47 STSpedHGG_RTK1AMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass A (novel)Yes48 STSpedHGG_RTK1CMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass C (novel)Yes49 STSCTRL_HEMIMC Control tissue, cerebral hemisphereNo	42	STS	GBM_RTK2	MC Glioblastoma, IDH-wild-type, RTK2 subtype	Yes				
45 STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes46 STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes47 STSpedHGG_RTK1AMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass A (novel)Yes48 STSpedHGG_RTK1CMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass C (novel)Yes49 STSCTRL_HEMIMC Control tissue, cerebral hemisphereNo	43	STS	GBM_RTK2	MC Glioblastoma, IDH-wild-type, RTK2 subtype	Yes				
46 STSGBM_RTK2MC Glioblastoma, IDH-wild-type, RTK2 subtypeYes47 STSpedHGG_RTK1AMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass A (novel)Yes48 STSpedHGG_RTK1CMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass C (novel)Yes49 STSCTRL_HEMIMC Control tissue, cerebral hemisphereNo	44	STS	GBM_RTK2	MC Glioblastoma, IDH-wild-type, RTK2 subtype	Yes				
47 STSpedHGG_RTK1AMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass A (novel)Yes48 STSpedHGG_RTK1CMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass C (novel)Yes49 STSCTRL_HEMIMC Control tissue, cerebral hemisphereNo	45	STS	GBM_RTK2	MC Glioblastoma, IDH-wild-type, RTK2 subtype	Yes				
48 STSpedHGG_RTK1CMC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass C (novel)Yes49 STSCTRL_HEMIMC Control tissue, cerebral hemisphereNo	46	STS	GBM_RTK2	MC Glioblastoma, IDH-wild-type, RTK2 subtype	Yes				
49 STS CTRL_HEMI MC Control tissue, cerebral hemisphere No	47	STS	pedHGG_RTK1A	MC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass A (novel)	Yes				
	48	STS	pedHGG_RTK1C	MC Diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass C (novel)	Yes				
50 STS PXA MC Pleomorphic xanthoastrocytoma No	49	STS	CTRL_HEMI	MC Control tissue, cerebral hemisphere	No				
	50	STS	PXA	MC Pleomorphic xanthoastrocytoma	No				

The last column shows whether the patients was included in the analysis, based on the methylation classification. H3, histone 3; ID, patient study number; IDH, isocitrate dehydrogenase; MC, methylation class; RTK, receptor tyrosine kinase.

 Table 3.
 Glioblastoma (GBM) subtype, methylation status for 06-methylguanine methyltransferase (MGMT), and leukocytes unmethylation for purity (LUMP) score for long-term survivors (LTS) and short-term survivors (STS) with a confirmed IDH-wild-type GBM

I1LTSClassicalMethylated0,8019412LTSClassicalMethylated0,6369513LTSClassicalUnmethylated0,6792914LTSClassicalMethylated0,6792915LTSNAUnmethylated0,6759816LTSNAMethylated0,742626STSMesenchymalUnmethylated0,6424727STSMesenchymalUnmethylated0,6297628STSMesenchymalUnmethylated0,6297629STSMesenchymalUnmethylated0,6297630STSMesenchymalUnmethylated0,267431STSMesenchymalUnmethylated0,267433STSMesenchymalUnmethylated0,426434STSMesenchymalUnmethylated0,426435STSMesenchymalUnmethylated0,426436STSProneuralMethylated0,4375136STSProneuralMethylated0,538936STSProneuralUnmethylated0,555637STSProneuralUnmethylated0,558439STSProneuralUnmethylated0,558439STSProneuralUnmethylated0,558439STSProneuralUnmethylated0,65249314STSProneuralUnmethylated0,6574315ProneuralUnmethylated<	ID	Group	GBM subtype	MGMT status	LUMP score
3 LTS Mesenchymal Methylated 0,58812 4 LTS Mesenchymal Methylated 0,66676 5 LTS Mesenchymal Unmethylated 0,46122 7 LTS Mesenchymal Methylated 0,46122 7 LTS Mesenchymal Methylated 0,4612 8 LTS Mesenchymal Methylated 0,4897 9 LTS Proneural Methylated 0,4897 10 LTS Classical Methylated 0,80401 11 LTS Classical Methylated 0,80491 12 LTS Classical Methylated 0,80994 13 LTS Classical Unmethylated 0,67999 14 LTS NA Unmethylated 0,67991 15 LTS NA Unmethylated 0,67926 16 LTS NA Unmethylated 0,62471 27 STS Mesenchymal Un	1	LTS	Mesenchymal	Methylated	0,49301
44 LTS Mesenchymal Methylated 0,65676 5 LTS Mesonchymal Unmethylated 0,31907 6 LTS Mesonchymal Methylated 0,46122 7 LTS Mesonchymal Methylated 0,46123 8 LTS Mesonchymal Methylated 0,4897 9 LTS Mesonchymal Methylated 0,4897 10 LTS Classical Methylated 0,8041 11 LTS Classical Methylated 0,80491 12 LTS Classical Methylated 0,80491 13 LTS Classical Methylated 0,80491 14 LTS Classical Methylated 0,82081 15 LTS NA Methylated 0,82081 16 LTS NA Methylated 0,82081 17 STS Mesonchymal Umethylated 0,82081 18 LTS Mesonchymal <t< td=""><td>2</td><td>LTS</td><td>Mesenchymal</td><td>Methylated</td><td>0,55363</td></t<>	2	LTS	Mesenchymal	Methylated	0,55363
5 LTS Mesenchymal Unmethylated 0,31907 6 LTS Mesenchymal Methylated 0,46122 7 LTS Mesenchymal Methylated 0,46122 7 LTS Mesenchymal Methylated 0,4612 8 LTS Proneural Methylated 0,80401 10 LTS Classical Methylated 0,80401 11 LTS Classical Methylated 0,80401 12 LTS Classical Methylated 0,63695 13 LTS Classical Methylated 0,67598 14 LTS Classical Unmethylated 0,67598 15 LTS NA Unmethylated 0,62076 16 LTS NA Unmethylated 0,62427 17 STS Mesenchymal Unmethylated 0,62976 16 LTS Mesenchymal Unmethylated 0,42674 17 STS Mesenchymal	3	LTS	Mesenchymal	Methylated	0,58812
6 LTS Mesenchymal Methylated 0.46122 7 LTS Mesenchymal Methylated 0.4415 8 LTS Mesenchymal Methylated 0.4897 9 LTS Proneural Methylated 0.72869 100 LTS Classical Methylated 0.80194 111 LTS Classical Methylated 0.80994 12 LTS Classical Methylated 0.82088 133 LTS Classical Methylated 0.67929 144 LTS Classical Methylated 0.67929 155 LTS NA Unmethylated 0.67929 166 LTS NA Methylated 0.64247 175 Mesenchymal Unmethylated 0.62976 186 STS Mesenchymal Unmethylated 0.62976 187 Mesenchymal Unmethylated 0.62976 180 STS Mesenchymal Unmethylated	4	LTS	Mesenchymal	Methylated	0,65676
7 LTS Mesenchymal Methylated 0,4415 8 LTS Mesenchymal Methylated 0,4897 9 LTS Proneural Methylated 0,2897 100 LTS Classical Methylated 0,80401 11 LTS Classical Methylated 0,8095 12 LTS Classical Methylated 0,63695 13 LTS Classical Unmethylated 0,63695 13 LTS Classical Methylated 0,67929 14 LTS NA Unmethylated 0,67938 15 LTS NA Unmethylated 0,7426 16 LTS NA Unmethylated 0,4277 STS Mesenchymal Unmethylated 0,42767 28 STS Mesenchymal Unmethylated 0,42674 29 STS Mesenchymal Unmethylated 0,42674 20 STS Mesenchymal Unmethylated	5	LTS	Mesenchymal	Unmethylated	0,31907
8 LTS Mesenchymal Methylated 0,4897 9 LTS Proneural Methylated 0,72869 10 LTS Classical Methylated 0,80194 11 LTS Classical Methylated 0,80194 12 LTS Classical Methylated 0,63695 13 LTS Classical Methylated 0,67292 14 LTS Classical Methylated 0,67293 15 LTS Classical Methylated 0,67293 16 LTS NA Unmethylated 0,67294 15 LTS NA Unmethylated 0,67297 16 LTS NA Unmethylated 0,64247 17 STS Mesenchymal Unmethylated 0,64247 16 LTS Mesenchymal Unmethylated 0,4267 17 STS Mesenchymal Unmethylated 0,4267 18 STS Mesenchymal <td< td=""><td>6</td><td>LTS</td><td>Mesenchymal</td><td>Methylated</td><td>0,46122</td></td<>	6	LTS	Mesenchymal	Methylated	0,46122
9 LTS Proneural Methylated 0,72869 100 LTS Classical Methylated 0,80401 111 LTS Classical Methylated 0,80491 12 LTS Classical Methylated 0,83695 13 LTS Classical Unmethylated 0,67929 13 LTS Classical Methylated 0,82088 15 LTS Classical Methylated 0,82088 15 LTS NA Unmethylated 0,67598 16 LTS NA Methylated 0,62208 17 NA Methylated 0,64247 26 STS Mesenchymal Unmethylated 0,62976 27 STS Mesenchymal Unmethylated 0,62976 28 STS Mesenchymal Unmethylated 0,42674 38 STS Mesenchymal Unmethylated 0,42674 39 STS Mesenchymal Unmethylated </td <td>7</td> <td>LTS</td> <td>Mesenchymal</td> <td>Methylated</td> <td>0,4415</td>	7	LTS	Mesenchymal	Methylated	0,4415
10LTSClassicalMethylated0,8040111LTSClassicalMethylated0,8019412LTSClassicalMethylated0,6399513LTSClassicalUnmethylated0,6792914LTSClassicalMethylated0,6793815LTSNAUnmethylated0,6759816LTSNAMethylated0,6424726STSMesenchymalUnmethylated0,6424727STSMesenchymalUnmethylated0,6297828STSMesenchymalUnmethylated0,6297829STSMesenchymalUnmethylated0,6297629STSMesenchymalUnmethylated0,6297629STSMesenchymalUnmethylated0,6297620STSMesenchymalUnmethylated0,6297630STSMesenchymalUnmethylated0,4267432STSMesenchymalUnmethylated0,4267433STSProneuralUnmethylated0,4375134STSProneuralUnmethylated0,4375135STSProneuralUnmethylated0,6191136STSProneuralUnmethylated0,6194136STSProneuralUnmethylated0,6324937STSProneuralUnmethylated0,6324938STSProneuralUnmethylated0,6324939STSProneural <td>8</td> <td>LTS</td> <td>Mesenchymal</td> <td>Methylated</td> <td>0,4897</td>	8	LTS	Mesenchymal	Methylated	0,4897
I1LTSClassicalMethylated0,8019412LTSClassicalMethylated0,6369513LTSClassicalUmmethylated0,6792914LTSClassicalMethylated0,8208815LTSNAUmmethylated0,6798916LTSNAMethylated0,742626STSMesenchymalUmmethylated0,6424727STSMesenchymalUmmethylated0,6596628STSMesenchymalUmmethylated0,6297629STSMesenchymalUmmethylated0,6297630STSMesenchymalUmmethylated0,6297631STSMesenchymalUmmethylated0,6297633STSMesenchymalUmmethylated0,4267434STSMesenchymalUmmethylated0,4267435STSMesenchymalUmmethylated0,4267436STSProneuralMethylated0,4267437STSProneuralMethylated0,538938STSProneuralUmmethylated0,5384936STSProneuralUmmethylated0,555639STSProneuralUmmethylated0,5584939STSProneuralUmmethylated0,65249314STSProneuralUmmethylated0,65249315ProneuralUmmethylated0,65249316STSProneuralUmmethyl	9	LTS	Proneural	Methylated	0,72869
12LTSClassicalMethylated0,6369513LTSClassicalUnmethylated0,6792914LTSClassicalMethylated0,8208815LTSNAUnmethylated0,759816LTSNAMethylated0,742626STSMesenchymalUnmethylated0,6424727STSMesenchymalUnmethylated0,6297628STSMesenchymalUnmethylated0,6297629STSMesenchymalUnmethylated0,6297629STSMesenchymalUnmethylated0,6297620STSMesenchymalUnmethylated0,4267421STSMesenchymalUnmethylated0,4267422STSMesenchymalMethylated0,4267423STSMesenchymalMethylated0,4307524STSProneuralMethylated0,4375125STSProneuralMethylated0,4375126STSProneuralMethylated0,4375127STSProneuralMethylated0,5384928STSProneuralMethylated0,5384929STSProneuralMethylated0,5384929STSProneuralMethylated0,5384929STSProneuralUnmethylated0,5384929STSProneuralUnmethylated0,6374920STSProneuralUnmethylat	10	LTS	Classical	Methylated	0,80401
ITS Classical Unmethylated 0,67929 14 LTS Classical Methylated 0,82088 15 LTS NA Unmethylated 0,67598 16 LTS NA Methylated 0,7426 26 STS Mesenchymal Unmethylated 0,62427 27 STS Mesenchymal Unmethylated 0,62976 28 STS Mesenchymal Unmethylated 0,62976 29 STS Mesenchymal Unmethylated 0,62976 30 STS Mesenchymal Unmethylated 0,42674 31 STS Mesenchymal Unmethylated 0,42674 32 STS Mesenchymal Methylated 0,42674 33 STS Mesenchymal Unmethylated 0,42674 34 STS Mesenchymal Unmethylated 0,42674 35 STS Proneural Unmethylated 0,54991 36 STS Proneural	11	LTS	Classical	Methylated	0,80194
H4LTSClassicalMethylated0,8208815LTSNAUnmethylated0,6759816LTSNAMethylated0,742626STSMesenchymalUnmethylated0,6424727STSMesenchymalUnmethylated0,6297628STSMesenchymalUnmethylated0,6297629STSMesenchymalUnmethylated0,6297630STSMesenchymalUnmethylated0,4807531STSMesenchymalMethylated0,4807533STSMesenchymalMethylated0,4807534STSMesenchymalMethylated0,4807535STSMesenchymalUnmethylated0,4807536STSProneuralUnmethylated0,4807536STSProneuralUnmethylated0,4807536STSProneuralUnmethylated0,4807537STSProneuralUnmethylated0,6109138STSProneuralUnmethylated0,5584939STSProneuralUnmethylated0,6524939STSProneuralUnmethylated0,6524939STSProneuralUnmethylated0,6524939STSProneuralUnmethylated0,6524939STSProneuralUnmethylated0,6524939STSProneuralUnmethylated0,6524930STSClassical <td>12</td> <td>LTS</td> <td>Classical</td> <td>Methylated</td> <td>0,63695</td>	12	LTS	Classical	Methylated	0,63695
15 LTS NA Unmethylated 0,67598 16 LTS NA Methylated 0,7426 26 STS Mesenchymal Unmethylated 0,64247 27 STS Mesenchymal Unmethylated 0,65096 28 STS Mesenchymal Unmethylated 0,62976 29 STS Mesenchymal Unmethylated 0,48075 29 STS Mesenchymal Unmethylated 0,48075 30 STS Mesenchymal Unmethylated 0,48075 31 STS Mesenchymal Unmethylated 0,48075 32 STS Mesenchymal Methylated 0,42674 33 STS Mesenchymal Unmethylated 0,48075 34 STS Mesenchymal Methylated 0,48075 35 STS Proneural Methylated 0,34751 36 STS Proneural Methylated 0,5566 37 STS Proneural Unmethylated 0,55567 38 STS Pron	13	LTS	Classical	Unmethylated	0,67929
16 LTS NA Methylated 0,7426 26 STS Mesenchymal Unmethylated 0,64247 27 STS Mesenchymal Unmethylated 0,5096 28 STS Mesenchymal Unmethylated 0,62976 29 STS Mesenchymal Unmethylated 0,62976 29 STS Mesenchymal Unmethylated 0,48075 30 STS Mesenchymal Unmethylated 0,42674 31 STS Mesenchymal Methylated 0,42674 32 STS Mesenchymal Unmethylated 0,42674 33 STS Mesenchymal Unmethylated 0,42674 34 STS Mesenchymal Unmethylated 0,42674 35 STS Mesenchymal Unmethylated 0,43071 36 STS Proneural Methylated 0,34751 37 STS Proneural Unmethylated 0,61041 38 STS Proneural Unmethylated 0,61041 39 STS	14	LTS	Classical	Methylated	0,82088
Abs STS Mesenchymal Unmethylated 0,64247 277 STS Mesenchymal Unmethylated 0,47079 288 STS Mesenchymal Unmethylated 0,55096 299 STS Mesenchymal Unmethylated 0,62976 300 STS Mesenchymal Unmethylated 0,42674 31 STS Mesenchymal Methylated 0,42674 32 STS Mesenchymal Methylated 0,42674 33 STS Mesenchymal Unmethylated 0,42674 34 STS Mesenchymal Unmethylated 0,42674 33 STS Mesenchymal Unmethylated 0,42674 34 STS Proneural Methylated 0,43751 34 STS Proneural Unmethylated 0,4358 35 STS Proneural Unmethylated 0,5556 36 STS Proneural Unmethylated 0,61741 36 <t< td=""><td>15</td><td>LTS</td><td>NA</td><td>Unmethylated</td><td>0,67598</td></t<>	15	LTS	NA	Unmethylated	0,67598
27 STS Mesenchymal Unmethylated 0,47079 28 STS Mesenchymal Unmethylated 0,55096 29 STS Mesenchymal Unmethylated 0,62976 30 STS Mesenchymal Unmethylated 0,48075 31 STS Mesenchymal Methylated 0,42674 32 STS Mesenchymal Methylated 0,42674 33 STS Mesenchymal Unmethylated 0,42674 34 STS Mesenchymal Unmethylated 0,42674 35 STS Mesenchymal Unmethylated 0,42674 36 STS Mesenchymal Unmethylated 0,43751 37 STS Proneural Methylated 0,73158 38 STS Proneural Unmethylated 0,61091 38 STS Proneural Unmethylated 0,51561 39 STS Proneural Unmethylated 0,61741 40 STS Proneural Unmethylated 0,63249 41 STS	16	LTS	NA	Methylated	0,7426
R8STSMesenchymalUnmethylated0,5509629STSMesenchymalUnmethylated0,6297680STSMesenchymalUnmethylated0,4807581STSMesenchymalMethylated0,4267482STSMesenchymalMethylated0,4267483STSMesenchymalMethylated0,4267484STSMesenchymalUnmethylated0,4267483STSMesenchymalUnmethylated0,4267484STSProneuralMethylated0,3475185STSProneuralMethylated0,3475186STSProneuralMethylated0,4335886STSProneuralMethylated0,5384987STSProneuralUnmethylated0,5586189STSProneuralUnmethylated0,6324981STSProneuralUnmethylated0,6324981STSClassicalUnmethylated0,6872482STSClassicalUnmethylated0,6872483STSClassicalUnmethylated0,6878184STSClassicalUnmethylated0,621985STSClassicalUnmethylated0,621986STSClassicalUnmethylated0,621987STSClassicalUnmethylated0,621988STSClassicalUnmethylated0,621989STSClassical	26	STS	Mesenchymal	Unmethylated	0,64247
P3STSMesenchymalUnmethylated0,6297680STSMesenchymalUnmethylated0,4807581STSMesenchymalMethylated0,4267482STSMesenchymalMethylated0,5489183STSMesenchymalUnmethylated0,3475184STSProneuralMethylated0,7315885STSProneuralMethylated0,4367886STSProneuralMethylated0,6109187STSProneuralUnmethylated0,5384988STSProneuralUnmethylated0,555689STSProneuralUnmethylated0,6324981STSProneuralUnmethylated0,6324981STSClassicalUnmethylated0,6872482STSClassicalUnmethylated0,6872483STSClassicalUnmethylated0,6872484STSClassicalUnmethylated0,6878184STSClassicalUnmethylated0,6279184STSClassicalUnmethylated0,6279185STSClassicalUnmethylated0,6279386STSClassicalUnmethylated0,6279186STSClassicalUnmethylated0,6279186STSClassicalUnmethylated0,6279387STSClassicalUnmethylated0,6279388STSClassic	27	STS	Mesenchymal	Unmethylated	0,47079
80STSMesenchymalUnmethylated0,4807581STSMesenchymalMethylated0,4267482STSMesenchymalMethylated0,5489183STSMesenchymalUnmethylated0,3475184STSProneuralMethylated0,7315885STSProneuralMethylated0,4267486STSProneuralMethylated0,3475187STSProneuralMethylated0,7315886STSProneuralMethylated0,6109187STSProneuralUnmethylated0,5384988STSProneuralUnmethylated0,555689STSProneuralUnmethylated0,6324981STSProneuralUnmethylated0,6872482STSClassicalUnmethylated0,6872483STSClassicalUnmethylated0,6878184STSClassicalMethylated0,6266785STSClassicalUnmethylated0,62266784STSClassicalUnmethylated0,6273984STSClassicalUnmethylated0,6273985STSClassicalUnmethylated0,6273986STSClassicalUnmethylated0,6273986STSClassicalUnmethylated0,6273987STSClassicalUnmethylated0,6273988STSSTSCl	28	STS	Mesenchymal	Unmethylated	0,55096
STSMesenchymalMethylated0,4267432STSMesenchymalMethylated0,5489133STSMesenchymalUnmethylated0,3475134STSProneuralMethylated0,7315835STSProneuralMethylated0,4835836STSProneuralMethylated0,6109137STSProneuralUnmethylated0,5384938STSProneuralUnmethylated0,555639STSProneuralUnmethylated0,6174140STSProneuralUnmethylated0,6324941STSProneuralUnmethylated0,6324942STSClassicalUnmethylated0,6878143STSClassicalUnmethylated0,8266744STSClassicalUnmethylated0,8266745STSClassicalUnmethylated0,6273946STSClassicalUnmethylated0,62739	29	STS	Mesenchymal	Unmethylated	0,62976
32STSMesenchymalMethylated0,5489133STSMesenchymalUnmethylated0,3475134STSProneuralMethylated0,7315835STSProneuralMethylated0,4835836STSProneuralMethylated0,6109137STSProneuralUnmethylated0,5349938STSProneuralUnmethylated0,555639STSProneuralUnmethylated0,6174140STSProneuralUnmethylated0,6324941STSProneuralUnmethylated0,6824942STSClassicalUnmethylated0,6872443STSClassicalUnmethylated0,6878144STSClassicalUnmethylated0,6267146STSClassicalUnmethylated0,60739	30	STS	Mesenchymal	Unmethylated	0,48075
33STSMesenchymalUnmethylated0,3475134STSProneuralMethylated0,7315835STSProneuralMethylated0,4835836STSProneuralMethylated0,6109137STSProneuralUnmethylated0,5384938STSProneuralUnmethylated0,555639STSProneuralUnmethylated0,6174140STSProneuralUnmethylated0,6324941STSProneuralUnmethylated0,5583342STSClassicalUnmethylated0,6872443STSClassicalUnmethylated0,6872444STSClassicalUnmethylated0,6021946STSClassicalUnmethylated0,6021946STSClassicalUnmethylated0,67339	31	STS	Mesenchymal	Methylated	0,42674
B4STSProneuralMethylated0,73158B5STSProneuralMethylated0,48358B6STSProneuralMethylated0,61091B7STSProneuralUnmethylated0,53849B8STSProneuralUnmethylated0,5556B9STSProneuralMethylated0,61741B0STSProneuralUnmethylated0,63249B1STSProneuralUnmethylated0,63249B1STSProneuralUnmethylated0,68724B2STSClassicalUnmethylated0,68781B4STSClassicalUnmethylated0,82667B5STSClassicalUnmethylated0,60219B6STSClassicalUnmethylated0,60219	32	STS	Mesenchymal	Methylated	0,54891
STSProneuralMethylated0,4835836STSProneuralMethylated0,6109137STSProneuralUnmethylated0,5384938STSProneuralUnmethylated0,555639STSProneuralMethylated0,6174140STSProneuralUnmethylated0,6324941STSProneuralUnmethylated0,6324942STSClassicalUnmethylated0,6872443STSClassicalUnmethylated0,6872444STSClassicalMethylated0,622946STSClassicalUnmethylated0,6229	33	STS	Mesenchymal	Unmethylated	0,34751
36STSProneuralMethylated0,6109137STSProneuralUnmethylated0,5384938STSProneuralUnmethylated0,555639STSProneuralMethylated0,6174140STSProneuralUnmethylated0,6324941STSProneuralUnmethylated0,6324942STSClassicalUnmethylated0,6872443STSClassicalUnmethylated0,6872444STSClassicalUnmethylated0,6878145STSClassicalUnmethylated0,626746STSClassicalUnmethylated0,60219	34	STS	Proneural	Methylated	0,73158
B7STSProneuralUnmethylated0,53849B8STSProneuralUnmethylated0,5556B9STSProneuralMethylated0,61741B0STSProneuralUnmethylated0,63249B1STSProneuralUnmethylated0,63249B1STSProneuralUnmethylated0,68724B2STSClassicalUnmethylated0,68724B3STSClassicalUnmethylated0,68781B4STSClassicalUnmethylated0,6267B5STSClassicalUnmethylated0,60219B6STSClassicalUnmethylated0,67339	35	STS	Proneural	Methylated	0,48358
88STSProneuralUnmethylated0,555689STSProneuralMethylated0,6174140STSProneuralUnmethylated0,6324941STSProneuralUnmethylated0,5858342STSClassicalUnmethylated0,6872443STSClassicalUnmethylated0,6878144STSClassicalMethylated0,6267345STSClassicalUnmethylated0,621946STSClassicalUnmethylated0,67339	36	STS	Proneural	Methylated	0,61091
STSProneuralMethylated0,6174140STSProneuralUnmethylated0,6324941STSProneuralUnmethylated0,5858342STSClassicalUnmethylated0,6872443STSClassicalUnmethylated0,6878144STSClassicalMethylated0,8266745STSClassicalUnmethylated0,6021946STSClassicalUnmethylated0,67339	37	STS	Proneural	Unmethylated	0,53849
A0STSProneuralUnmethylated0,63249A1STSProneuralUnmethylated0,58583A2STSClassicalUnmethylated0,68724A3STSClassicalUnmethylated0,68781A4STSClassicalUnmethylated0,68781A5STSClassicalMethylated0,62671A5STSClassicalUnmethylated0,60219A6STSClassicalUnmethylated0,60339	38	STS	Proneural	Unmethylated	0,5556
A1STSProneuralUnmethylated0,58583A2STSClassicalUnmethylated0,68724A3STSClassicalUnmethylated0,68781A4STSClassicalMethylated0,82667A5STSClassicalUnmethylated0,60219A6STSClassicalUnmethylated0,67339	39	STS	Proneural	Methylated	0,61741
12STSClassicalUnmethylated0,6872413STSClassicalUnmethylated0,6878114STSClassicalMethylated0,8266715STSClassicalUnmethylated0,6021916STSClassicalUnmethylated0,67339	40	STS	Proneural	Unmethylated	0,63249
I3STSClassicalUnmethylated0,68781I4STSClassicalMethylated0,82667I5STSClassicalUnmethylated0,60219I6STSClassicalUnmethylated0,67339	41	STS	Proneural	Unmethylated	0,58583
I4STSClassicalMethylated0,82667I5STSClassicalUnmethylated0,60219I6STSClassicalUnmethylated0,67339	42	STS	Classical	Unmethylated	0,68724
15STSClassicalUnmethylated0,6021916STSClassicalUnmethylated0,67339	43	STS	Classical	Unmethylated	0,68781
16 STS Classical Unmethylated 0,67339	44	STS	Classical	Methylated	0,82667
	45	STS	Classical	Unmethylated	0,60219
	46	STS	Classical	Unmethylated	0,67339
	47		Proneural	Unmethylated	
18 STS Proneural Methylated 0,63177	48		Proneural	Methylated	
ID, patient study number; NA, not available.	ID natient st	udv.number: NA_not available			

ID, patient study number; NA, not available.

Some other studies (n = 18-55) found that some genes are more common in LTS, but did not reach the level of being statistically significant: EGFR,²⁰TP53,^{20,21} and PTEN.²¹ In our study, the homozygous deletion of CDKN2A/B was significantly more present in the STS group, which is in line with CDKN2A/B loss that has been described as a prognostic factor for a worse outcome in IDH-mutant glioma³¹ and in IDH-wild-type GBM.^{14,15}

Following our CpG analysis, we identified differentially methylated genes between LTS versus STS. Subsequently,

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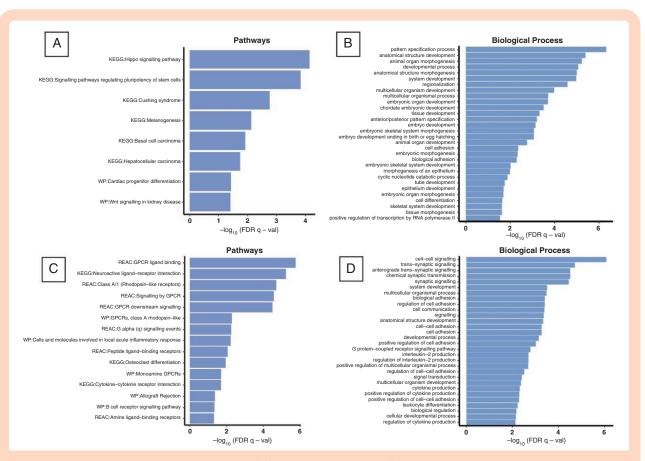


Figure 1. Upregulated pathways in long-term survivors (A) and in short-term survivors (C), and involved biological processes in long-term survivors (B) and short-term survivors (D).

we identified upregulated pathways in LTS and in STS. The most common upregulated pathway in LTS is the Hippo signaling pathway. This pathway is involved in many different cancers, such as renal cell carcinoma, non-small cell lung cancer, and breast cancer. In GBM, this pathway is involved in cell proliferation, migration, invasiveness, and chemotherapy resistance.³² Most genes involved in the Hippo pathway are tumor suppressor genes, which explains why it is upregulated in our LTS group. In more detail, when this pathway is downregulated, the next step in the cascade Yes-Associated Protein/Transcriptional Co-activator with PDZ-binding motif (YAP/TAZ) is active and promotes cell growth and inhibits apoptosis. Conversely, when the Hippo pathway is upregulated, YAP/ TAZ remains inactive.³³ Moreover, the Hippo pathway has many interactions with other pathways, including the Wnt pathway (another upregulated pathway in our LTS group), which, in addition, to its own role in stem cell maintenance, tumor growth, and invasion, stimulates the Hippo signaling pathway. The Wnt pathway was also found in LTS of a recent trial in GBM in the elderly (Nordic phase 3 trial).³⁴ It is unclear in humans, however, why the Hippo and Wnt pathways were upregulated in LTS. In a recent mouse model, a decreased activity of the Wnt pathway was associated with an increased delivery of temozolomide.35

In our STS group, G-protein-coupled receptors (GPCR) were the most upregulated pathway. GPCRs represent a large family of cell-surface molecules involved in signal transduction. In various cancers, including breast cancer, small cell lung cancer, and ovarian cancer, many GPCRs are upregulated.³⁶ This upregulation leads to stimulated cell growth, proliferation, and angiogenesis. In GBM, a decreased expression of *ING4*, a candidate tumor suppressor gene, leads to upregulation of interleukin 8 (IL8), which stimulates angiogenesis, and subsequently tumor progression via GPCR pathways.³⁷

The strength of this study derives from a relatively large cohort of sex- and age-matched patients with GBM who survived more than 5 years. Additionally, patients were collected from 2 different centers and comprehensive patient and treatment data were complete. Moreover, comprehensive methylation data including methylation-based diagnostic classification, CNV analysis, and gene analysis were performed. However, due to the retrospective nature of this study, there are several limitations. Most importantly, some FFPE samples of LTS were no longer available because samples were destroyed after the legal duration for storage has passed. As a result, some clinical information (eg, performance status at baseline, recurrences, etc.) was missing in some LTS. Although we describe a relatively large group of LTS, the sample size is modest and comparable leuro-Oncol Idvances to previously reported studies.9,20,21,23 Our findings have not been validated in an external cohort. The methylation classifier rendered nontumor diagnoses, based on the analyzed FFPE sample. This discrepancy with the histological diagnosis could be explained due to the analyzed sample which contained more nontumor cells than tumor cells. Moreover, some samples date back to the era before temozolomide was available and/or IDH testing was possible. Lastly, we excluded these samples in order to have a homogeneous group in the analysis of methylation differences. Larger, prospective studies are needed to confirm our results and to expand our knowledge of genetic and epigenetic changes in long-term GBM survivors. These efforts may also shed further insight into the pathogenesis of GBM and identify new molecular targets for therapeutic intervention. Notably, an ongoing large, international prognostic study of long-term (ie, >5 years) GBM patients (n = 189), the ETERNITY study, addresses these questions.⁷

In conclusion, few patients with an IDH-wild-type GBM survive more than 5 years, and some clinical LTS GBM patients can be shown to have an alternative diagnosis upon methylation profiling. This study highlights differences in a cohort of methylation-confirmed GBM and describes some differences in methylation patterns of gene expression and pathways between long-term and short-term GBM survivors.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (https://academic.oup.com/neuro-oncology).

Keywords

glioblastoma | long-term survivors | methylation | pathway analysis

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Conflict of interest statement

None declared.

Authorship statement

Collection of the data: R.C.R., S.A.C., N.K., R.O., K.A., P.D., and D.M.; analyzing the data: M.v.d.M., M.R.V., V.P., Q.W., and O.S.;

interpretation of the data: all authors; first draft of the manuscript: M.v.d.M. and M.R.V.; revision of the manuscript: all authors; supervision of the study: G.Z. and W.P.M.

Data availability

All data have been collected and stored at University Health Network and are available anonymously upon request (https://www.zadehlab.com/biobank/).

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