Association of the *FGFR1* mutation with spontaneous hemorrhage in low-grade gliomas in pediatric and young adult patients

Yukitomo Ishi, MD,¹ Shigeru Yamaguchi, MD,¹ Kanako C. Hatanaka, MD,² Michinari Okamoto, MD,¹ Hiroaki Motegi, MD,¹ Hiroyuki Kobayashi, MD,^{1,3} Shunsuke Terasaka, MD,^{1,3} and Kiyohiro Houkin, MD^{1,3}

¹Department of Neurosurgery, Hokkaido University School of Medicine, Kita-ku, Sapporo; ²Department of Surgical Pathology, Hokkaido University Hospital, Kita-ku, Sapporo; and ³Department of Neurosurgery, Kashiwaba Neurosurgical Hospital, Toyohira-ku, Sapporo, Hokkaido, Japan

OBJECTIVE The authors aimed to investigate genetic alterations in low-grade gliomas (LGGs) in pediatric and young adult patients presenting with spontaneous hemorrhage.

METHODS Patients younger than 30 years of age with a pathological diagnosis of World Health Organization (WHO) grade I or II glioma and who had undergone treatment at the authors' institution were retrospectively examined. *BRAF* V600E, *FGFR1* N546/K656, *IDH1* R132, *IDH2* R172, and *KIAA1549-BRAF* (K-B) fusion genetic alterations were identified, and the presence of spontaneous tumoral hemorrhage was recorded.

RESULTS Among 66 patients (39 with WHO grade I and 27 with grade II tumors), genetic analysis revealed K-B fusion in 18 (27.3%), *BRAF* V600E mutation in 14 (21.2%), *IDH1/2* mutation in 8 (12.1%), and *FGFR1* mutation in 4 (6.1%). Spontaneous hemorrhage was observed in 5 patients (7.6%); 4 of them had an *FGFR1* mutation and 1 had K-B fusion. Univariate analysis revealed a statistically significant association of an *FGFR1* mutation and a diencephalic location with spontaneous hemorrhage. Among 19 diencephalic cases including the optic pathway, hypothalamus, and thalamus, an *FGFR1* mutation was significantly associated with spontaneous hemorrhage ($p < 0.001$). Four *FGFR1* mutation cases illustrated the following results: 1) a 2-year-old female with pilomyxoid astrocytoma (PMA) harboring the *FGFR1* K656E mutation presented with intraventricular hemorrhage (IVH); 2) a 6-year-old male with PMA harboring *FGFR1* K656E and D652G mutations presented with intratumoral hemorrhage (ITH); 3) a 4-year-old female with diffuse astrocytoma harboring *FGFR1* K656M and D652G mutations presented with IVH; and 4) a young adult patient with pilocytic astrocytoma with the *FGFR1* N546K mutation presented with delayed ITH and IVH after 7 years of observation.

CONCLUSIONS Although the mechanism remains unclear, the *FGFR1* mutation is associated with spontaneous hemorrhage in pediatric and young adult LGG.

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KEYWORDS *FGFR1*; *BRAF*; hemorrhage; low-grade glioma; pediatric; young adult; oncology

MOST pilocytic astrocytomas (PAs) exhibit genetic alterations in *BRAF*, with either missense mutation of V600E or *KIAA1549-BRAF* (K-B) fusion.² Cerebellar hemisphere PAs typically harbor K-B fusion, while both *BRAF* V600E and K-B fusion are frequent in supratentorial cases.² K-B fusion is primarily observed in PA,³¹ whereas the *BRAF* V600E mutation is observed in PA as well as other low-grade gliomas (LGGs), such as ganglioglioma and pleomorphic xanthoastrocytoma.²¹

After *BRAF* alterations, hotspot mutations of N546 or K656 in *FGFR1* are the second most common major genetic alteration in PA.¹⁰ *FGFR1* and *BRAF* participate in mitogen-activated protein kinase (MAPK) signaling.¹⁰ An *FGFR1* mutation as well as *BRAF* alterations cause activation of MAPK signaling, which drives the development of PA.¹⁰ Missense mutation and tyrosine kinase domain (TKD) duplication of *FGFR1* are also frequent in dysembryoplastic neuroepithelial tumor (DNT), pediatric oligo-

ABBREVIATIONS DA = diffuse astrocytoma; DNT = dysembryoplastic neuroepithelial tumor; ITH = intratumoral hemorrhage; IVH = intraventricular hemorrhage; K-B fusion = *KIAA1549-BRAF* fusion; LGG = low-grade glioma; MAPK = mitogen-activated protein kinase; PA = pilocytic astrocytoma; PCR = polymerase chain reaction; PMA = pilomyxoid astrocytoma; TKD = tyrosine kinase domain; WHO = World Health Organization.

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TABLE 1. Summary of pediatric and young adult LGGs with the *FGFR1* mutation

Case	Age at Onset (yrs)	Sex	Location	Pathology	Genetic Alteration	Type of Bleeding	Timing of Bleeding
1	2	F	Hypothalamus	PMA	<i>FGFR1</i> p.K656E	IVH	Onset
2	6	M	Thalamus	PMA	<i>FGFR1</i> p.K656E + p.D652G	ITH	Onset
3	4	F	Hypothalamus	DA	<i>FGFR1</i> p.K656M + p.D652G	IVH	Onset
4	19	M	Hypothalamus	PA	<i>FGFR1</i> p.N546K	ITH + IVH	Delayed
5	15	F	Cerebellar	PA	<i>K-B</i> (ex16_ex11) fusion	ITH	Onset

dendrogloma, and rosette-forming glioneuronal tumor.^{5,20} Therefore, an *FGFR1* mutation is important in pediatric and young adult LGGs, as is *BRAF* alteration.

Spontaneous hemorrhage is a rare clinical event in patients with LGG, including PA.^{22,27} Nonetheless, spontaneous hemorrhage can be lethal despite a benign tumor pathology;^{4,27} therefore, predictive risk factors should be determined. Little is known about tumor-specific genetic risk factors for spontaneous hemorrhage in LGG, despite recent progress in glioma genomic research. In this study, we identified a high incidence of *FGFR1* mutation in pediatric and young adult LGGs with spontaneous hemorrhage.

Methods

Patient Population

In this retrospective study, we included all patients younger than 30 years of age with World Health Organization (WHO) grade I and II gliomas who had undergone treatment at Hokkaido University Hospital between 2002 and 2019. Pathological diagnosis was based on the WHO Classification of Tumours of the Central Nervous System. Patient data including clinical course, treatment outcome, radiological imaging findings, and pathological findings were retrospectively analyzed. Institutional review board approval was obtained; as this study was retrospective, the requirement for informed consent was waived.

Genetic Analysis

DNA/RNA was extracted from frozen tumor tissue using the AllPrep DNA/RNA Mini kit (Qiagen) or from a formalin-fixed paraffin-embedded (FFPE) block using the ReliaPrep FFPE gDNA Miniprep system (Promega) and RNAsort kit (Cell Data Sciences). First-strand cDNA was synthesized using a PrimeScript II 1st strand cDNA Synthesis kit (Takara) in accordance with the manufacturer's recommendations. Mutation hotspots at codon 132 of *IDH1*, codon 172 of *IDH2*, codon 600 of *BRAF*, and codon 546 of exon 12 and codon 656 of exon 14 of *FGFR1* were screened using Sanger sequencing. Genomic DNA was amplified by polymerase chain reaction (PCR) using Quick Taq HS DyeMix (Toyobo). The oligonucleotide primers used for PCR were as follows: forward primer for *IDH1*, TGTGGAAATCACCAATGGCAC; reverse primer for *IDH1*, TACAAGTTGGAAATTTCTGGGC; forward primer for *IDH2*, GGGAGCCCATCATCTGCA AAAA; reverse primer for *IDH2*, ACAAGAGGATGG CTAGGCGA; forward primer for *BRAF*,¹⁵ TGCTTGCTC TGATAGGAAAATG; reverse primer for *BRAF*,¹⁵ TGA

TGGGACCCACTCCAT; forward primer for *FGFR1* exon 12, CTTTAAAGCGGACGCAACA; reverse primer for *FGFR1* exon 12, GATACCCCAGCTCAGATCTTCTC; forward primer for *FGFR1* exon 14, AGGAATGTCCTG GTGACAGA; and reverse primer for *FGFR1* exon 14, CCACTCCTTGCTTCTCAGAT. Because almost all missense mutations in *FGFR1* occur in exon 12 or 14,^{10,20} we performed mutation screening of *FGFR1* exclusively in these two exons. Cycle sequencing was conducted with the BigDye Terminator v3.1 Cycle Sequencing kit (Applied Biosystems) using forward and reverse PCR primers as sequencing primers. Sequencing data were obtained using the Genetic Analyzer 3130 Avant (Applied Biosystems). *K-B* fusion was screened by reverse transcriptase PCR using previously described primer sets.¹¹

Statistical Analysis

Statistical analysis using Fisher's exact test was performed with EZR software (Saitama Medical Centre, Jichi Medical University, <http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html>; Kanda, 2012), which is a graphical user interface for R (version 2.13.0, R Foundation for Statistical Computing). A value of $p < 0.05$ was considered statistically significant.

Results

Spontaneous Hemorrhage in Pediatric and Young Adult LGGs

Sixty-six patients (39 with WHO grade I and 27 with grade II tumors) were included in this study. Five (7.6%) developed spontaneous hemorrhage during the follow-up period; 4 of these cases presented acutely, and 1 presented in a delayed fashion (Table 1). The frequency of spontaneous hemorrhage was 5.1% and 11.1% in WHO grade I and II tumors, respectively. Location of the tumor was midline, including the hypothalamus and thalamus, in 4 cases. Genetic analysis revealed an *FGFR1* mutation in 4 cases and *K-B* fusion in 1 case. Because an *FGFR1* mutation was frequent in the hemorrhagic cases, we present 4 such cases below.

Case Presentations

Case 1

This female patient was initially treated for intraventricular hemorrhage (IVH) at the age of 2 years (Fig. 1A). Since then, she has been bed-ridden with severe neurological deficits. Although MRI was not performed at the

FIG. 1. Case 1. **A:** Head CT obtained when the patient was 2 years of age, showing IVH. **B:** Head CT obtained 2 months after hemorrhage, revealing cerebral infarction in the left hemisphere and a mass lesion in the left hypothalamic region (arrow). **C:** Gd-enhanced T1-weighted MR image obtained at age 4 years, showing tumor with heterogeneous enhancement in the left hypothalamus. **D:** Left carotid artery DSA revealed abnormal vasculature fed by the anterior choroidal artery. **E:** H & E staining of the biopsy specimen at the first operation revealed a pathological diagnosis of anaplastic astrocytoma with densely proliferating astrocytic tumor cells and oligodendroglial tumor cells (inset). Original magnification $\times 10$. **F:** H & E staining of the specimen at the second operation due to regrowth of residual tumor revealed a pathological diagnosis of PMA, based on a pilomyxoid background and angiocentric pattern. Original magnification $\times 20$.

time, serial CT revealed a mass lesion in the posthemorrhagic cavity as the hemorrhage had resolved (Fig. 1B). At the age of 4 years, she was referred to our institution because of a newly observed tumor at the hemorrhage site. MRI revealed a tumor in the left hypothalamus (Fig. 1C), and DSA revealed abnormal vessels supplied from the left anterior choroidal artery (Fig. 1D). She underwent surgical biopsy, and the pathological diagnosis was anaplastic oligoastrocytoma (Fig. 1E). She received chemotherapy consisting of a single course of cisplatin (CDDP) and etoposide (VP-16), followed by a course of carboplatin (CBDCA) and VP-16 and radiotherapy (25.2 Gy of whole craniospinal radiation and 25.2 Gy of local radiation). She then underwent another resection for residual tumor; the pathological diagnosis was pilomyxoid astrocytoma (PMA; Fig. 1F). Because the first surgical specimen was very small for pathological diagnosis and the pathological findings of the second surgical specimen were typical for PMA, we believe that the pathological findings of the first specimen were part of the whole tumor pathology;

therefore, PMA was established as the final diagnosis. No vascular abnormality was identified in either the first or second surgical specimen. The patient underwent 2 additional courses of chemotherapy with CBDCA and vincristine (VCR); however, she died at the age of 5 years as a result of local progression and dissemination of the tumor. Genetic analysis showed the *FGFR1* K656E mutation in both the biopsy specimen and the resective operation.

Case 2

This male patient presented with the sudden onset of headache and vomiting at the age of 6 years. Because brain MRI showed an intracranial tumor, he was referred to our institution. Preoperative CT and MRI showed intratumoral hemorrhage (ITH) in the suprasellar region (Fig. 2A–B). DSA revealed no abnormal vascular structures (Fig. 2C). He underwent emergent surgery for tumor resection. The pathological diagnosis was PMA (Fig. 2D), and genetic analysis showed *FGFR1* D652G and K656E mutations. No vascular abnormality was pathologically

FIG. 2. Case 2. **A:** Initial head CT showing a high-density mass in the suprasellar region. **B:** Gd-enhanced T1-weighted MR image showing tumor with heterogeneous enhancement in the right hypothalamus. **C:** Bilateral carotid artery DSA (R = right, L = left) demonstrating no apparent vascular abnormality. **D:** H & E staining of the tumor specimen revealed a pathological diagnosis of PMA, based on the pilomyxoid background and angiocentric pattern. Original magnification $\times 20$.

identified. He underwent 6 courses of chemotherapy with CDDP and VCR and local radiation with 50.4 Gy. He remains alive without neurological deterioration or tumor recurrence at 11 years.

Case 3

This female patient was referred to another hospital due to sudden headache and vomiting at the age of 4 years. Head CT showed IVH and she underwent ventricular drainage (Fig. 3A). She was then referred to our institution after MRI showed a brain tumor in the left thalamus (Fig. 3B). Stereotactic biopsy of the tumor was performed. The pathological diagnosis was diffuse astrocytoma (DA; Fig. 3C), and genetic analysis showed *FGFR1* D652G and K656M mutations. No vascular abnormality was pathologically identified. She underwent local radiation with 46 Gy. She remains alive without neurological deficit or tumor recurrence at 19 years.

Case 4

This 19-year-old male presented with visual disturbance in his right eye. MRI showed a suprasellar tumor (Fig. 4A), and he underwent craniotomy for partial re-

section. The pathological diagnosis was PA, and genetic analysis revealed the *FGFR1* N546K mutation (Fig. 4B). No vascular abnormality was pathologically identified. Considering his age, the patient was observed and not provided adjuvant treatment. Although the tumor showed repeated growth and shrinkage on serial imaging, he did not develop a neurological deficit over about 6 years after surgery. However, he then presented with coma 2 months after the last MRI study. Head CT showed massive ITH and IVH (Fig. 4C). Three-dimensional CTA showed no evidence of vascular abnormality (Fig. 4D). The patient underwent emergent ventricular drainage but remains comatose.

Genetic Landscape and Spontaneous Hemorrhage in Pediatric and Young Adult LGGs

Sixty-six patients underwent genetic analysis for *BRAF*, *FGFR1*, and *IDH1/2* (Fig. 5). *K-B* fusion was detected in 18 patients (27.3%), and the *BRAF* V600E mutation was detected in 14 (21.2%), frequently in WHO grade I gliomas. The *IDH1/2* mutation was detected in 8 patients (12.1%), all in WHO grade II gliomas. An *FGFR1* mutation was detected in 4 patients (6.1%). Spontaneous hem-

FIG. 3. Case 3. **A:** Initial head CT showing IVH. **B:** FLAIR MR image showing tumor with high intensity in the left thalamus. **C:** H & E staining of the biopsy specimen revealed a pathological diagnosis of DA, based on diffusely invading astrocytic tumor cells. Original magnification $\times 20$.

orrhage was observed in 55.6% of patients with *K-B* fusion and in 100% of those with *FGFR1* mutations. None of the patients with the *BRAF* mutation, the *IDH* mutation, or wild-type *BRAF/FGFR1/IDH* presented with spontaneous hemorrhage. Univariate analysis revealed a statistically significant association of an *FGFR1* mutation and a diencephalic location with spontaneous hemorrhage (Table 2). Among 19 diencephalic cases including the optic pathway, hypothalamus, and thalamus, an *FGFR1* mutation was significantly associated with spontaneous hemorrhage ($p < 0.001$; Table 3).

Discussion

Clinical Characteristics of LGGs With an *FGFR1* Mutation

Previous reports have indicated that the incidence of an *FGFR1* mutation is 5.2%–6.7% in PA,^{1,10} 36.4% in DNT,²⁰ 10% in oligodendroglioma,²⁰ and 46.2%–50% in

rosette-forming glioneuronal tumor.^{5,14} Our results suggest that *FGFR1* mutation is also observed in pediatric and young adult cases of DA and PMA. All 4 cases harboring an *FGFR1* mutation in our study were located in the thalamus and hypothalamus, which is consistent with previous reports of PA.¹⁰ Although the *FGFR1* mutation is associated with a poor prognosis in PA,¹ our cases had a significantly different outcome, suggesting clinical heterogeneity with respect to the *FGFR1* mutation.

Despite the fact that the *FGFR1* mutation has been observed in several types of LGG, the pathological findings of case 1 were unusual. Previous studies have suggested that PA and PMA lacking the classic pathological features could be diagnosed as several other types of tumors.^{2,7}

Spontaneous Hemorrhage in LGGs

Spontaneous hemorrhage has been observed in 8.0%–24.0% of PA and PMA cases.^{16,22,28} Histologically, a high

FIG. 4. Case 4. **A:** Preoperative MR image obtained when the patient was 19 years old, showing suprasellar tumor. **B:** H & E staining of the biopsy specimen revealed a pathological diagnosis of PA, based on a myxoid background and biphasic pattern with sparsely accumulating piloid tumor cells and densely accumulating tumor cells. Original magnification $\times 20$. **C:** Head CT scans obtained when the patient was 26 years old, showing massive ITH and IVH. **D:** Three-dimensional CTA showed no evidence of vascular abnormality.

frequency of hemorrhage in PMA cases has been reported.^{12,16} Although several risk factors for hemorrhage have been described, a recent large study on optic pathway–hypothalamic gliomas with spontaneous hemorrhage could not establish any risk factors.²⁷ In addition, a review of cerebellar PAs with hemorrhage did not clarify the pathophysiology of hemorrhage.⁴

Previous authors have reported that 2 (5.9%) of 34 optic pathway gliomas with hemorrhage have occurred in pregnant women.^{27,30} Because no cases of pregnancy were included in the present study, it is not certain whether pregnancy is a risk factor for spontaneous hemorrhage in gliomas. Moreover, degenerative vascular changes, abnormal vasculature, or amyloid vessels have been reported as causes of spontaneous hemorrhage,^{17,23,28} but these factors were not applicable in our study as no hemorrhagic cases presented with pathological vasculature abnormality. Previous reports have stated that the absence of pathological findings indicative of spontaneous hemorrhage is not uncommon.^{6,13,19,24} As regards angiographic findings, Suzuki et al. have reported the case of a diencephalic PA presenting with no vascular abnormality on DSA.²⁵ Although 1

case in this study presented with vascular abnormality on DSA, such cases would be relatively rare among hemorrhagic cases.²⁷

To the best of our knowledge, no previous studies have described an association between spontaneous hemorrhage and specific genetic alterations in a large number of patients. Wilson et al. have reported 2 cases of cerebellar PA in which genetic analysis was performed for *BRAF* V600E mutation and *K-B* fusion; however, these genetic alterations were not detected in these 2 cases.²⁹ Although a large number of patients with LGG such as PA presenting with hemorrhage have been reported,^{19,27} most patients have not undergone genetic analysis. This study shows a correlation between the *FGFR1* mutation and spontaneous hemorrhage in LGGs in pediatric and young adult patients. Our data also indicated the predominance of hemorrhage in diencephalic cases, which has not been previously reported in the literature. As *FGFR1*-mutated PAs frequently arise in midline locations, including the diencephalon,¹⁰ we consider that the predominance of hemorrhage in diencephalic cases and *FGFR1* mutation would be confounding factors in this study.

FIG. 5. Spontaneous hemorrhage and genetic landscape of LGGs. Spontaneous hemorrhage was observed in 5 cases of LGG, including 4 harboring an *FGFR1* mutation and 1 harboring *K-B* fusion.

Other Genetic Alterations in *FGFR1*

Genetic alterations in TKD duplication or missense mutation in *FGFR1* have been frequently reported in DNTs.²⁰ Although several cases of DNT with spontaneous hemorrhage have been described,²⁶ previous studies have demonstrated a relatively low frequency, with 2%–6.3% of hemorrhage cases in DNT.^{3,18} As our study included only

1 case with DNT, the correlation between genetic alteration and hemorrhage in DNT was uncertain. In diencephalic LGGs harboring the *BRAF* alteration of *K-B* fusion or V600E mutation, clinical differences between these groups have been reported despite the genetic alterations in the same gene.^{7,8} To the best of our knowledge, no previous study has analyzed the association between genetic alterations and hemorrhage in DNT; therefore, further investigation on TKD duplication and missense mutation in *FGFR1* is warranted for DNTs.

Genotype-Phenotype Correlation of *FGFR1* Mutation and Spontaneous Hemorrhage

The mechanism regarding how the *FGFR1* mutation re-

TABLE 2. Univariate analysis of associations with spontaneous hemorrhage using Fisher's exact test

Factor	OR	95% CI	p Value
Age < 15 yrs	1.04	0.11–13.31	0.99
Location			
Supratentorial	1.80	0.16–93.69	0.99
Midline	6.43	0.59–333.18	0.15
Diencephalic	12.67	0.002–0.95	<0.05
PA/PMA pathology	3.80	0.35–196.7	0.36
Genetic alteration			
<i>K-B</i> fusion	1.54	0.14–80.49	0.99
<i>FGFR1</i>	Inf	0.00–0.17	<0.000001

Inf = infinite.

Boldface type indicates statistical significance ($p < 0.05$).

TABLE 3. Correlation of *FGFR1* status and spontaneous bleeding among 19 diencephalic cases

<i>FGFR1</i> Mutation	Spontaneous Bleeding	
	+	–
Mutant	4	0
Wild type	0	15

+ = yes; – = no.

$p < 0.001$, Fisher's exact test.

sults in spontaneous hemorrhage is unclear. Radiological and pathological examinations did not suggest the presence of abnormal vessels that could cause spontaneous hemorrhage. Shibahara et al. reported that Ki-67 labeling index and microvascular proliferation were not statistically different between hemorrhagic and nonhemorrhagic cases of PA.²² Activation of the MAPK signaling pathway is commonly observed in LGGs such as PA.⁹ Because FGFR1 acts as an upstream protein to BRAF in MAPK signaling,¹⁰ we speculate that other effects in the signaling pathway due to an *FGFR1* mutation cause a biological difference compared with that in *BRAF*-altered cases. We believe that the presence of potential confounding factors must also be considered in this study. To confirm the significance of an *FGFR1* mutation in spontaneous hemorrhage, validation with a study involving a larger number of patients would be required.

Conclusions

Although the mechanism remains unclear, the association of an *FGFR1* mutation with spontaneous hemorrhage in pediatric and young adult LGG is suggested based on the results of this study. Because the specific mechanism remains unclear, the molecular function of an *FGFR1* mutation for tumor hemorrhage should be clarified.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

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Correspondence

Shigeru Yamaguchi: Hokkaido University Graduate School of Medicine, Sapporo, Japan. yama-shu@med.hokudai.ac.jp.