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Case Report

Familial schwannomatosis carrying *LZTR1* variant p.R340X with brain tumor: A case report

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ABSTRACT

Schwannomatosis (SWN) is a rare genetic condition characterized by the risk of developing multiple benign peripheral nerve sheath tumors; however, the risk of developing malignant tumors in patients with SWN remains unclear. This study described the case of a 57-year-old Japanese man diagnosed with SWN whose older brother also had SWN. Whole-exome sequencing identified a heterozygous mutation [c.1018C > T (p.Arg340X)] in the *LZTR1* gene, linked to the RAS/MAPK pathway, in the patient and his brother. Moreover, the patient had aphasia and right-sided paralysis because of a brain tumor. RNA sequencing revealed the remarkable upregulation of several genes associated with oxidative stress, such as the reactive oxygen species pathway and oxidative phosphorylation, a downstream effector of the RAS/MAPK pathway, in the the patient and his brother compared with healthy volunteers. The final diagnosis was *LZTR1*-related familial SWN, and the dysregulated RAS/MAPK pathway in this patient might be associated with brain tumorigenesis.

1. Introduction

Neurofibromatosis (NF) is an autosomal dominant genetic disorder characterized by tumorigenesis in the nervous system, including the brain, spinal cord, and peripheral nerves [1]. NF is classified as follows: NF type 1 (NF1 also known as von Recklinghausen disease or peripheral NF; OMIM#613113), NF2-related schwannomatosis (NF2: formerly known as NF type 2; OMIM#607379), and schwannomatosis (SWN; OMIM#162091 and OMIM#615670). NF1 is the most prevalent type, with an estimated incidence of 1 in 3000 births. NF2 and SWN are rare, with an estimated incidence of 1 in 33,000 and 1 in 70,000 births, respectively [2,3]. Patients with NF1 have a shorter life expectancy compared with the general population (median age 54.4 versus 70.1 years) because of malignant tumors and vascular diseases [4]. Patients with NF2 have an average life span of 36 years [5]. Bilateral vestibular schwannomas characterize NF2. While patients with NF develop brain tumors, such as meningiomas and ependymomas, the risk of malignant tumors in patients with SWN remains unclear [6,7].

Apart from multiple benign peripheral nerve tumors, most patients with NF1 have specific cutaneous manifestations, such as light-brown patches of skin pigmentation (known as cafe-au-lait spots), multiple flats, skinfold freckling, visible neurofibromas under the skin, and small nodules in the iris [1]. A few patients with NF2 also have cutaneous features similar to those with NF1; however, patients with SWN exhibit no such features [8]. These three types of NF have traditionally been differentiated based on their clinical manifestations [6,9,10]. The clinical diagnostic guidelines for SWN recommend molecular testing to diagnose SWN accurately [11–13]. Mutations in two tumor suppressor genes, namely, SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily b, member 1 (*SMARCB1*) and leucine zipper-like transcription regulator 1 (*LZTR1*), have been considered as the cause of SWN [1,11–13]. Germline mutations of the

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SMARCB1 or *LZTR1* gene occur in 85% of familial and 40% of sporadic patients [1,11–13]. Based on a meta-analysis, malignant nerve tumors occur primarily due to the germline pathogenic variants of the *SMARCB1* gene [14]. Meanwhile, more data are needed to predict the tumorigenesis and clinical management of *LZTR1*-related SWN.

This study presents an adult patient with familial SWN who had a concomitant diffuse brain tumor. Molecular testing demonstrated a pathogenic loss-of-function (LOF) mutation of the *LZTR1* gene in the patient and his brother, suggesting that RAS/MAPK pathway dysregulation was the main mechanism of brain tumorigenesis.

2. Case presentation

A 57-year-old man presented to our emergency department because of aphasia and difficulty standing, with 2 months of progressive right-sided muscle weakness. His past medical history was unremarkable, and he had not been regularly receiving any medication. His older brother had undergone surgery for schwannoma arising from cervical spinal nerve 4 in the Department of Orthopedics at our institution.

Upon arrival, his Glasgow Coma Scale score was 12 (E4V2M6). His body temperature, heart rate, blood pressure level, and oxygen saturation were 37.9 °C, 122 beats per minute, 187/135 mmHg, and 98% in room air, respectively. Upon physical examination, his pupils were bilaterally mydriatic and reactive to light without pupillary fixation. He exhibited right-sided hemiparesis and conduction aphasia with unique jargon. Palpable subcutaneous masses were also found in his left forearm, behind the left thigh, and on the right leg. Moreover, light-brown pigmented spots on the skin were observed on his trunk and extremities (Fig. 1). These clinical findings suggested NF1 or NF2.

Laboratory examination revealed mild leukocytosis (white blood cell count of 12,300/μL), normocytic anemia (hemoglobin of 9.9 g/dL), and elevated levels of lactate dehydrogenase (340 U/mL). Furthermore, creatine kinase, creatinine (Cr), and blood urea nitrogen levels were 1478 U/L, 5.33 mg/dL, and 48.4 mg/dL, respectively. Urinalysis revealed proteinuria (2+) and hematuria (3+) (Supplementary Table 1).

Head computed tomography (CT) revealed a wide- and low-density area in the left parietal lobe (Fig. 2A and B). This finding suggested a brain tumor, such as glioblastoma or glioma, but not a stroke. Chest and abdominal CT revealed a nodule and masses in the left parietal pleura, in front of the left sacrum, and behind the left femur, along with bilateral hydronephrosis and hydroureter (Fig. 2C–F). Plain magnetic resonance imaging (MRI) of the brain revealed similar results to the head CT; however, nodules or masses were not detected (Fig. 2G).

The patient was immediately admitted to the Department of Emergency and Critical Care Medicine for further evaluation of the brain tumor and treatment of renal failure, suspected because of a neurogenic bladder as a complication of the brain tumor. Therefore, an indwelling urinary catheter was inserted, which indicated adequate urine output (approximately 1.0 mL/kg/h). However, Cr levels did not improve. Thus, to prevent the side effects of the gadolinium contrast agent, contrast-enhanced CT of the brain was performed to evaluate the brain tumor, which showed an enhanced small nodule in the left parietal lobe (Fig. 3). Although glioblastoma and glioma were first suspected, a brain biopsy was difficult for the following reasons: 1) because of the wide range of lesions, a random biopsy was not certain to yield a diagnosis; 2) the diagnosis was not considered clinically meaningful because renal failure would have precluded subsequent pharmacotherapy. A biopsy of the right leg mass established a histopathological diagnosis of schwannoma. Based on the clinical findings of multiple schwannomas and his family history, schwannoma-predisposing syndromes, particularly SWM, were suspected. To achieve a genetic diagnosis of familial SWN, whole-exome sequencing (WES) of this patient and his brother was performed [11–13]. Moreover, to identify transcriptome signatures associated with SWN, we performed RNA sequencing (RNA-Seq) analysis. All procedures were performed per the ethical standards of the Institutional Review Board of Wakayama Medical University (approval numbers 57 and 2910) and the tenets of the 1964 Helsinki Declaration and its later amendments.

The patient and his brother requested a transfer to a palliative care hospital. One month after admission to our hospital, the patient was transferred to another hospital with no improvement in symptoms. After the transfer, he survived peacefully in hospice care for more than one year. Based on the clinical course, diffuse low-grade glioma, such as diffuse astrocytoma, was suspected.

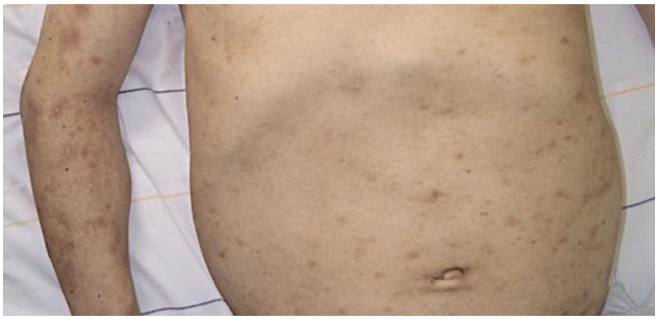

Fig. 1. Photograph of the patient showing multiple light-brown small skin pigments, but not typical cafe-au-lait spots, on the upper limb and trunk.

3. Materials and methods

3.1. Sample collection and DNA isolation

After obtaining written informed consent from all study participants, analyses were conducted. Peripheral blood mononuclear cells (PBMCs) were isolated using Ficoll solution (Histopaque-1077; Sigma-Aldrich, St Louis, MO, USA). Genomic DNA was extracted from PBMCs using the NucleoSpin Tissue kit (Macherey-Nagel, Duren, Germany).

3.2. WES analysis

WES identified genomic variants in the patient and his brother [15]. Sequencing libraries were prepared using the SureSelectXT Human All Exon V6 target enrichment system (Agilent Technologies, Santa Clara, CA, USA) and sequenced using the NovaSeq platform (Illumina, San Diego, CA, USA) with 150 bp + 150 bp paired-end sequencing cycles. The total number of reads obtained for the patient and his brother was 46,625,526 and 53,464,934, respectively. Raw FASTQ files were processed using Clara Parabricks workflow version 4.0.1–1 (NVIDIA, Santa Clara, CA, USA) with default settings for mapping to the hg19 human reference genome and variant detection in the genomic variant call format (GVCF). GVCF files for the patient and his brother were merged into a single variant call format (VCF) file using Glnexus software version 1.4.1 (Supplementary Table 2). The VCF file was annotated using ANNOVAR software and included GENCODE V33, ToMMo 8.3KJPN allele frequency in the Japanese population, and gnomAD version 2.1.1 exome-based allele frequency in the global population (Supplementary Table 2). Variants with altered amino acid sequences and allele frequencies $<0.05\%$ in 8.3KJPN and gnomAD were prioritized and examined manually. The raw data for WES analysis are listed in Supplementary Table 3 (individual gene-wise) and Supplementary Table 4 (individual variants).

In addition, Sanger sequencing confirmed the candidate variant detected by WES analysis within the patient and his brother. Supplementary Table 5 lists the primer sequences, and the sequencing results were read using Chromas software (version 2.22, Technelysium Pty, Ltd., South Brisbane, QLD, Australia).

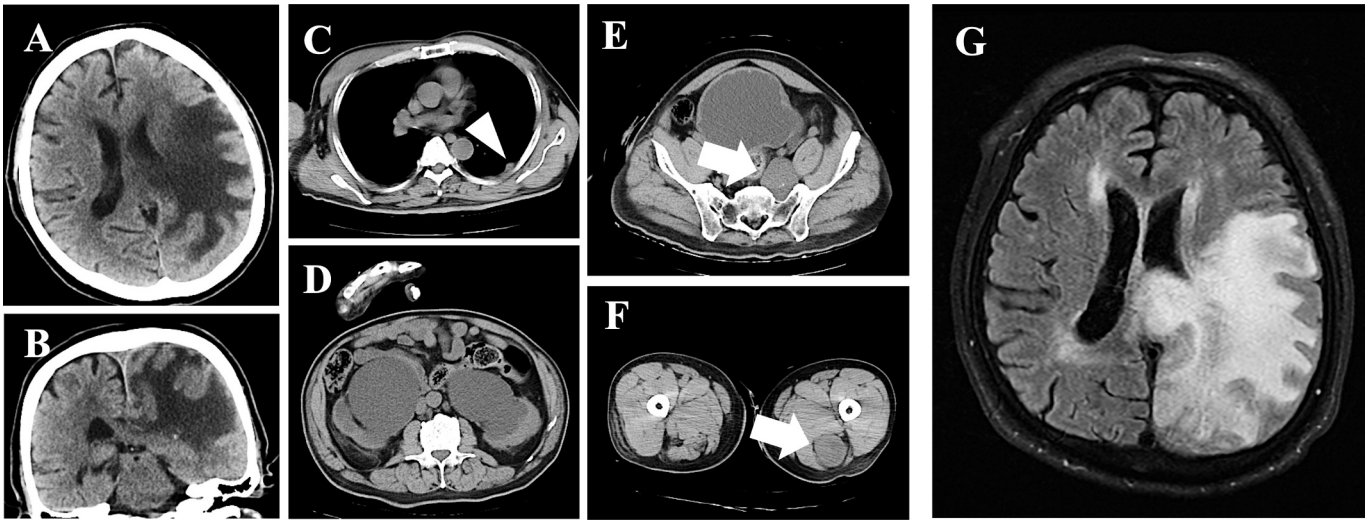

Fig. 2. Plain computed tomography (CT) and plain magnetic resonance imaging (MRI) findings of the patient upon admission. Plain CT showing an extensive low-density area in the left parietal lobe (A, B), nodular shadows in the left lateral pleura (C, arrowhead), bilateral hydronephrosis (D), and mass shadows in the left sacral anterior (E, arrow) and left posterior thigh (F, arrow). A plain brain MRI shows a mass lesion with strong and broad edema and mass effect in the left parietal lobe (G).

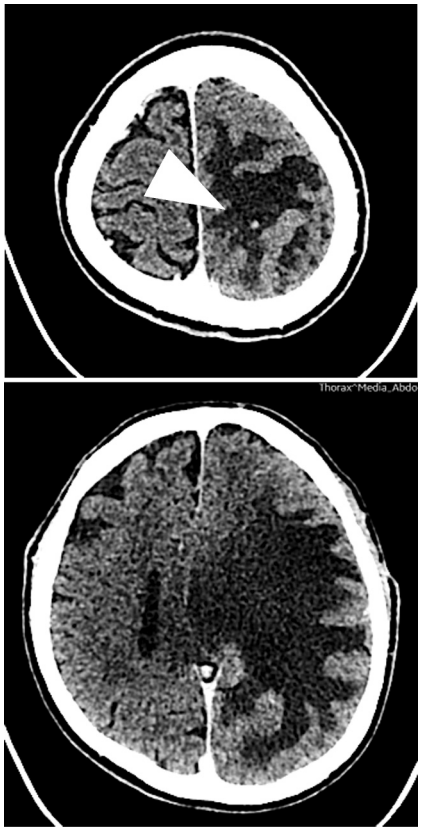

Fig. 3. Contrast-enhanced CT axial images of the brain showing the enhanced nodule (A, arrowhead) and strong cerebral edema surrounding this nodule (B).

3.3. RNA-Seq analysis

RNA-Seq analysis of PBMCs of the patient, his brother, and two healthy volunteers (with the same sex and age as the patient) was performed. Total RNA was extracted from PBMCs using the RNeasy Mini Kit (Qiagen, Hilden, Germany) per the manufacturer's instructions [16]. RNA quality was assessed using the Agilent 4200 TapeStation (Agilent Technologies, Inc., Santa Clara, CA, USA), and RNA concentration was measured using the Qubit Fluorometer (Thermo Fisher Scientific, Waltham, MA, USA). Sequencing libraries were constructed with 1500 ng of RNA from each sample using TruSeq Stranded mRNA (Illumina) per the manufacturer's protocol. cDNA was synthesized from the purified and fragmented mRNA. Single-index adapter ligation was also performed, and then the cDNA was amplified. The final concentration of sequence libraries was estimated using the KAPA Library Quantification Kit (Roche, Basel, Switzerland). The size of sequence libraries in the "Brother," "Patient," "Healthy 1," or "Healthy 2" samples was 348, 348, 343, or 331 base pairs, respectively. High-throughput sequencing of the samples was performed using the NextSeq 500/550 High Output Kit v2.5 (Illumina, 75 cycles pair-end, 40/40 cycles). The average number of sequence reads per sample of "Brother," "Patient," "Healthy 1," and "Healthy 2" was 24,121,057, 32,895,323, 16,782,611, and 22,249,343, respectively. The raw fastq files were analyzed using CLC Genomics Workbench version 12.0.2 (Filgen Inc., Nagoya, Japan; Supplementary Table 6). Supplementary Table 7 lists the raw transcript per million data. Clustergrammer analysis was performed using BioJupies (Supplementary Table 6) [17,18]. Gene set enrichment analysis (GSEA) was conducted using GSEA v4.2.3 software and the Molecular Signature Database (MSigDB) v7.5.1 (Supplementary Table 6) [19,20]. Normalized enrichment scores were calculated and ranked by the lower nominal *p*-value (NOM p-val), and pathways were upregulated using the hallmark gene sets in the SWN group ("Brother" and "Patient") compared with the healthy group ("Healthy 1" and "Healthy 2"). Supplementary Table 8 lists detailed GSEA information. The activated signaling pathways were visualized using the KEGG pathway database (Supplementary Table 6) [21].

4. Results

The genetic results arrived after the patient was transferred to the palliative care hospital. WES analysis identified a heterozygous nonsense mutation (c.1018C > T, p.Arg340X) in the substrate-binding domain (neighboring the fifth Kelch domain) of the *LZTR1* gene in two PBMCs (Fig. 4, arrow). Based on the recent diagnostic criteria, the patient and his brother were diagnosed with *LZTR1*-related SWN [11–13]. This genetic result was explained to his brother, who started his follow-up for the potential development of brain tumors.

Following RNA-Seq analysis, clustergrammer analysis showed the similarity of gene expression between PBMCs from the patient and his brother (Fig. 5A). GSEA was performed to determine the potential

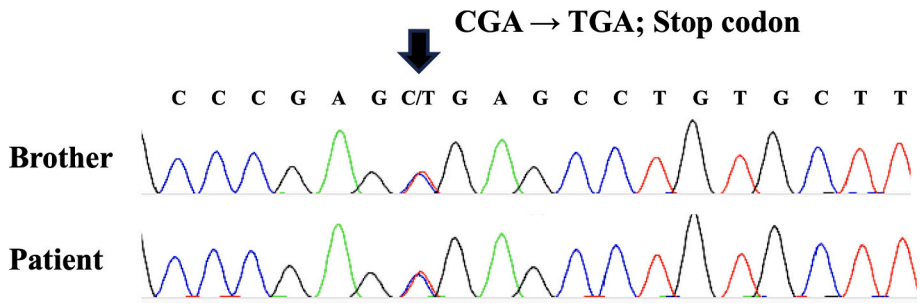

Fig. 4. Sanger sequencing results of the patient and his brother. An electropherogram of the *LZTR1* gene in the two individuals. A heterozygous C > T substitution was confirmed at position c.1018 (arrow), changing an arginine codon (CGA) into a stop codon (TGA) at amino acid position 340 (p.Arg340X).

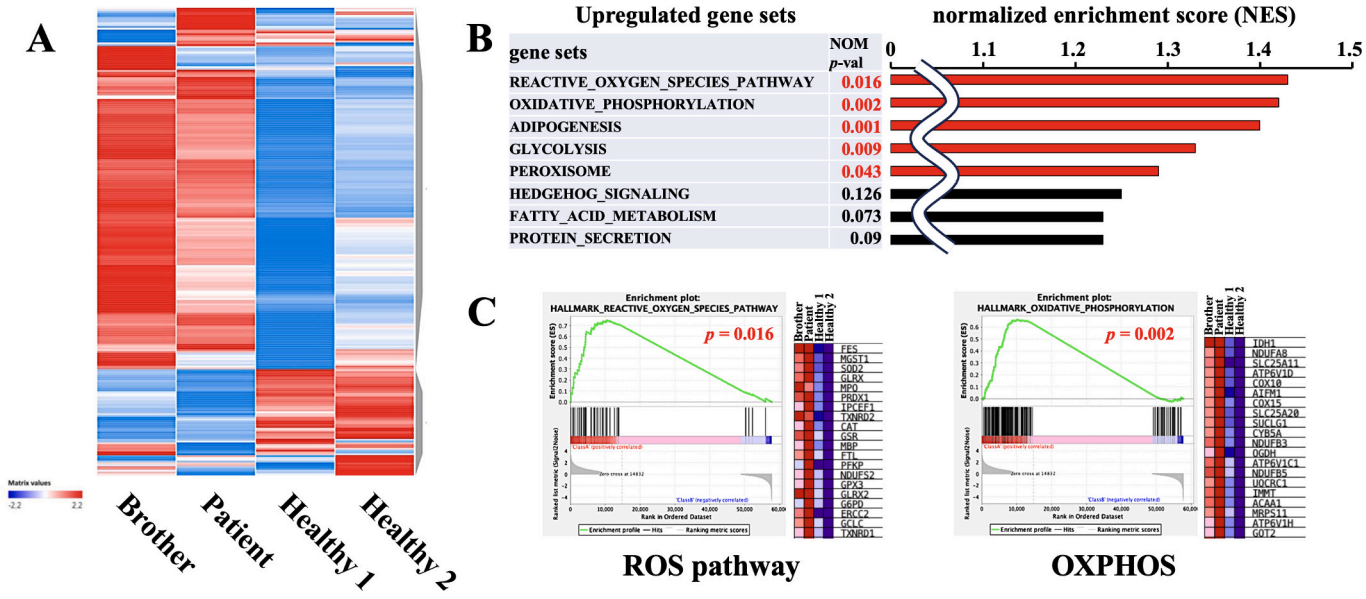

Fig. 5. (A) Clustergrammer analysis of the peripheral blood mononuclear cells from two individuals with *LZTR1*-related schwannomatosis (SWN) and two healthy volunteers. (B, C) Results of gene set enrichment analysis (GSEA). Normalized enrichment scores of the top 8 upregulated pathways using hallmark gene sets in the SWN group compared with the healthy group. Significantly upregulated gene sets are indicated by red bars (B). Enrichment plots for the ROS pathway- and oxidative phosphorylation (OXPHOS)-related gene sets. "*p*" indicates the nominal *p*-value (NOM *p*-val). Heatmap showing the changes in gene expression of the top 20 upregulated genes within the ROS pathway and OXPHOS gene sets (C).

functions of these differentially expressed genes. This analysis classified 46 gene sets as upregulated. The significantly upregulated gene sets were associated with the reactive oxygen species (ROS) pathway, oxidative phosphorylation (OXPHOS), adipogenesis, glycolysis, and peroxisomes (Fig. 5B). This study focused on the ROS pathway (normalized enrichment score = 1.43; nominal *p*-value = 0.016) and OXPHOS (normalized enrichment score = 1.42; nominal *p*-value = 0.002) in the upregulated gene sets (Fig. 5C and D, Supplementary Figs. 1 and 2). Based on these RNA-Seq data, the identified *LZTR1* variant induces gene signatures significantly associated with oxidative stress by activating the RAS/MAPK pathway.

5. Discussion

LZTR1 is a Golgi protein belonging to the BTB-Kelch superfamily. It plays a role in the polyubiquitination and degradation of RAS via the ubiquitin-proteasome pathway, which continuously activates the RAS/MAPK pathway [22,23]. WES identified a heterozygous nonsense mutation of the *LZTR1* gene in PBMCs of our patient and his brother. The variant represented a pathogenic LOF by mutation@A Glance (https://mutation.nagahama-i-bio.ac.jp/at_a_glance/), and this variant was predicted to disrupt the RAS/MAPK signaling pathway [24]. Furthermore, this variant has already been reported in two families with SWN [24]; however, the detailed clinical characteristics and disease are lacking.

Recent studies have indicated that germline LOF mutation in the *LZTR1* gene causes Noonan syndrome (NS) in up to 8% of such patients [25]. NS is a genetically inherited heterogeneous disease characterized by varying developmental delay, distinctive facial features, congenital cardiac abnormalities, and short stature. NS belongs to RASopathies, a group of developmental syndromes caused by germline mutations that encode RAS/MAPK pathway components [22,23]. RASopathies also include patients with germline mutations in the *NF1* gene, which negatively regulates RAS/MAPK signaling [26]. In some cases, the clinical manifestations of NF1 may mimic those of NS, and patients with NF1 exhibit an increased incidence of benign tumors and some malignancies, including glioblastoma and glioma [26]. A recent case report described an overlap of *LZTR1*-related NS with SWN and its clinical implications [27]. Although our patient had cutaneous findings, such as light-brown skin pigmentation spots, he did not present with other clinical characteristics of NF1 and NS. Therefore, during admission, these two genetic disorders were excluded.

The *LZTR1* gene was first identified as a tumor suppressor gene mutated in glioblastoma [26]. The loss of LZTR1 function by genetic mutation and deletion restricts self-renewal and growth of glioma spheres [28]. Two families with concomitant occurrence of *LZTR1*-

related SWN and glioblastoma have been reported [29]. However, no other occurrence of *LZTR1*-related SWN and malignant brain tumors has been reported to date. Meanwhile, *LZTR1*-related NS complicated with glioma has been recently reported [30]. Based on the imaging findings and clinical features of hemiparesis and aphasia, glioblastoma and glioma were suspected upon admission. The identified germline *LZTR1* mutation suggested the development of diffuse brain tumors, such as glioblastoma and glioma. A brain biopsy was not be performed on the patient because of the wide range of lesions and poor general condition. Accumulating tumor data is needed to further clarify the molecular mechanism of brain tumorigenesis in patients with *LZTR1*-related SWN.

RNA-seq analysis revealed a similar gene expression profile overall between the patient and his brother with SWN, compared with healthy volunteers. Moreover, GSEA indicated that these inducible genes, including the ROS pathway and OXPHOS, were strongly associated with oxidative stress. Enhanced oxidative stress in the body has been implicated in brain tumorigenesis, and the ROS pathway and OXYPHOS contribute to the development of glioblastoma and glioma [31]. Notably, *IDH1* and *IDH2* gene mutations are associated with OXPHOS, which could be an important early event during tumorigenesis [31]. Concerning OXPHOS, *IDH1* gene upregulation was observed in the patient and his brother. The RNA-seq data obtained in this study indicate that patients with *LZTR1*-related SWN are at high risk for developing brain tumors, such as glioblastoma and glioma, through persistent activation of the RAS/MAPK pathway. Therefore, close follow-up of the patient's brother for a potential brain tumor is warranted because of the presence of the same mutation in the *LZTR1* gene.

In general, patients with diffuse low-grade glioma survive with stable disease for years before dedifferentiation into a more malignant form [32,33]. These patients' median survival ranges between 5 and 10 years. Meanwhile, patients with glioblastoma have poor prognoses, with a median survival of only 10 to 14 months, although they receive combined treatment with radiotherapy [34]. After transferring to another hospital, the patient has survived with stable disease for more than one year. These clinical findings suggest that the patient had diffuse low-grade glioma but not glioblastoma.

6. Conclusions

This study presented the case of an adult patient with SWN who developed a brain tumor. Whole-exome analysis revealed a pathogenic LOF mutation in the *LZTR1* gene, which may be involved in dysregulating the RAS/MAPK pathway. Moreover, RNA-seq analysis revealed gene signatures associated with the development of brain tumors. This study is the first to perform transcriptome profiling analysis in patients with *LZTR1*-related SWN. Transcriptome profiling in adult patients with SWN can elucidate the pathogenesis and provide insights into appropriate management of secondary tumorigenesis.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2024.101107.

Ethics approval statement

This study was conducted by the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Wakayama Medical University (approval numbers: 57 and 2910, approved on July 31, 2015, and August 31, 2020, respectively).

Informed consent statement

Written informed consent was obtained from the patient's family to publish this paper.

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CRediT authorship contribution statement

Masaki Ibe: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Conceptualization. **Shinobu Tamura:** Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Hideki Kosako:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Yusuke Yamashita:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Masamichi Ishii:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Masaoh Tanaka:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Conceptualization. **Hiroyuki Mishima:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Akira Kinoshita:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Sadahiro Iwabuchi:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Shuhei Morita:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Koichiro Yoshiura:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Shinichi Hashimoto:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Naoyuki Nakao:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Shigeaki Inoue:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors have declared no competing interest.

Data availability

All data are included in the main text.

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