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BRIEF COMMUNICATION

T_2-FLAIR Mismatch Sign Is Caused by Long T_1 and T_2 of *IDH*-mutant, 1p19q Non-codeleted Astrocytoma

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T_2-fluid-attenuated inversion recovery images (FLAIR) mismatch sign is now known to be a specific yet insensitive image feature for *IDH*-mutant, 1p19q non-codeleted astrocytoma. The current study revealed that lesion presenting T_2-FLAIR mismatch exhibited extremely long T_1- and T_2-relaxation time while T_2-FLAIR matched lesions showed low to moderate values. On the other hand, *IDH*-wildtype tumors presented noticeably short T_1- and T_2-relaxation time. These different relaxation time characteristics seemed to render T_2-FLAIR mismatch sign of becoming such a unique and specific image feature for *IDH*-mutant, 1p19q non-codeleted astrocytoma.

Keywords: *T_2-fluid-attenuated inversion recovery images mismatch, relaxometry, IDH mutation, 1p19 codeletion*

Introduction

Genetic characterization of WHO grade 2 and 3 gliomas, namely lower-grade gliomas (LrGG), has become one of the crucial diagnostic workups for treating this neoplastic disorder.[1] With the desire to have preoperative determination of genetic characteristics of this disease, numerous efforts have attempted to identify imaging biomarkers that could be useful as surrogates of gene alterations of LrGG. During this effort, T_2-fluid-attenuated inversion recovery images (FLAIR) mismatch sign emerged as one of the promising imaging biomarkers for characterizing *IDH* mutation status of LrGG, which is a radiographical feature defined as "complete/near-complete hyperintense signal on T_2-weighted image (T_2WI) and relatively hypointense signal on FLAIR except for hyperintense peripheral rim".[2] Investigation of the Cancer Genome Atlas (TCGA)/Cancer Imaging Archive (TCIA) dataset discovered that the presence of T_2-FLAIR mismatch sign for LrGG was able to identify *IDH*-mutant, 1p19q non-codeleted tumors with a positive predictive value of 100 and negative predictive value of 54%. High specificity of T_2-FLAIR mismatch sign for identifying *IDH*-mutant, 1p19q non-codeleted tumors has been validated in several large cohorts.[2–6] Sensitivity, however, of T_2-FLAIR mismatch sign for *IDH*-mutant, 1p19q non-codeleted tumors is known to be relatively low. For example, one of the validation studies revealed that the sensitivity of T_2-FLAIR mismatch sign for *IDH*-mutant, 1p19q non-codeleted tumors was as low as 51%.[5] This finding could discourage relying on this radiographic feature on determination of genetic characteristics of LrGG and highlights the need for refining the method to improve currently low sensitivity. It should also be noted with care that tumor containing "T_2-FLAIR mismatch regions" cannot be defined as "T_2-FLAIR mismatch sign" unless they fulfil the criteria mentioned above. Although the underlining mechanism of T_2-FLAIR mismatch sign in *IDH*-mutant, 1p19q non-codeleted tumors is still unknown up to today, the presence of T_2-FLAIR mismatch could indicate that *IDH*-mutant, 1p19q non-codeleted tumors could possess tissues with relatively long T_1 relaxation time. In this brief communication, the authors investigated the relationship between genetic characteristics of LrGG and quantitative T_1 and T_2 relaxation time measurements (MR relaxometry) under 3T magnetic resonance imaging (MRI).

Materials and Methods

The local Institutional Ethical Review Board approved the use of clinical data for this research, and the authors obtained written informed consent from each patient (approval number 1306055036).

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Nine patients with histologically confirmed LrGG who have undergone T_1 and T_2 mapping as part of their preoperative workup were analyzed. Table 1 describes detailed patient characteristics. All cases were subjected to central pathology review by senior neuropathologists. Integrated diagnosis was made based on microscopic histological diagnosis and the status of *IDH*1/2 and 1p/19q copy number in compliance with the CNS WHO2016.[7]

There were two *IDH*-mutant, 1p19q non-codeleted tumor patients, two *IDH*-mutant, 1p19q codeleted tumor patients, and five *IDH*-wildtype tumor patients. A 3T MR scanner (Prisma; Siemens Healthcare, Erlangen, Germany) was utilized for T_1 and T_2 mapping. T_1-relaxometry was achieved by first acquiring MP2RAGE images, then converting those images into T_1-relaxation time maps while T_2-relaxometry was achieved by first acquiring multi-echo T_2-weighted images and then converting those images into T_2-relaxation time maps, with both relaxometries performed via Bayesian inference modeling (Olea Nova+; Canon Medical Systems, Tochigi, Japan).[8] MP2RAGE was acquired using: repetition time (TR) = 5000 ms; echo time (TE) = 3.86 ms; and inversion time (TI) = 935/2820 ms. Multi-echo T_2-weighted imaging was acquired using: TR = 4000 ms and TE = 20, 40, 60, 80, 100, 120 and 140 ms. T_2WI was acquired using: TR = 5000 ms and TE = 104 ms. Images were acquired in 256 × 256 matrix with a field of view (FOV) of 240 × 240 mm. Slice thickness was 3 mm with 0.3 mm spacing between slices. Measurement of T_1-relaxation time was limited up to 4300 ms due to technical constraint of Olea Nova+. Finally, FLAIR images was acquired using: TR = 10,000 ms; TE = 107 ms; and TI = 2700 ms (Image matrix = 226 × 384, FOV = 217 × 240 mm, slice thickness = 5 mm, slice spacing = 0.5 mm.).

T_2-weighted image and FLAIR were co-registered to T_1- and T_2-maps using normalized mutual information algorithm followed by visual confirmation of the registration. Voxels-of-interests (VOIs) were manually segmented by the first author who has 19 years of experience as a neurosurgeon and more than 10 years of experience as a surgical neuro-oncologist. VOIs were created based on high-intensity signals presented on FLAIR including all slices with pathological lesions. In the case of *IDH*-mutant, 1p19q non-codeleted tumor, two types of VOIs were created; i.e., one encompassing area with matched T_2-FLAIR high-intensity signal (T_2/FLAIR matched) and another with area exhibiting high-T_2 but low-FLAIR intensity signal (T_2/FLAIR mismatched). Finally, a scatter plot of T_2-relaxation time as a function of T_1-relaxation time was created according to each type of VOI.

Olea Nova+ reconstructed synthetic MRI using T_1- and T_2-maps experimenting TI = 2100 ms constraining TR to 10,000 ms and TE to 60 ms. We performed this procedure to examine whether it is possible or not to improve visualization of T_2-FLAIR mismatch sign by altering image acquisition parameters of FLAIR with particular interest in TI.

Results

As can be seen in Figs. 1 and 2, there was, in general, a positive linear correlation between T_1- and T_2-relaxation time within the presumed pathological lesion. As expected, lesion presenting T_2-FLAIR mismatch exhibited extremely long T_1- and T_2-relaxation time (Fig. 1 orange) while T_2-FLAIR matched lesions showed short to moderate T_1- and T_2-relaxation time (Fig. 1 green and Fig. 2). The difference of T_1- and T_2-relaxation time between these two lesions was statistically significant (unpaired *t*-test, $P < 0.0001$). Furthermore, *IDH*-wildtype tumors presented noticeably short T_1- and T_2-relaxation time (Figs. 2 and 3). When the scatter plot of T_1- versus T_2-relaxation time was compared between 1p19q codeleted and non-codeleted tumors among *IDH*-mutated tumors, a more extensive range of data distribution is noticed for the non-codeleted than for the codeleted tumors (Fig. 3). Synthetic FLAIR images were constructed to test the hypothesis that shortening TI could contribute to better visualization of T_2-FLAIR mismatch sign. As expected, lowing TI significantly improved visualization of areas that present

Table 1 Patient characteristics

Case ID	Sex	Age	Pathology	Molecular characteristics	T_2-FLAIR mismatch sign	T_2-FLAIR mismatch region
1	M	34	Diffuse astrocytoma	IDH-mt	Positive	Present
2	F	35	Anaplastic astrocytoma	IDH-mt	Negative	Slightly present
3	F	29	Oligodendroglioma	IDH-mt, 1p/19q-codeleted	Negative	None
4	M	30	Oligodendroglioma	IDH-mt, 1p/19q-codeleted	Negative	Very slightly present
5	F	81	Diffuse astrocytoma	IDH-wt	Negative	None
6	M	69	Anaplastic astrocytoma	IDH-wt	Negative	None
7	M	20	Ganglioglioma	IDH-wt	Negative	None
8	F	68	Anaplastic astrocytoma	IDH-wt	Negative	None
9	F	48	Diffuse midline glioma	IDH-wt, H3 K27M-mt	Negative	None

M, male; F, female; wt, wild type; mt, mutant.

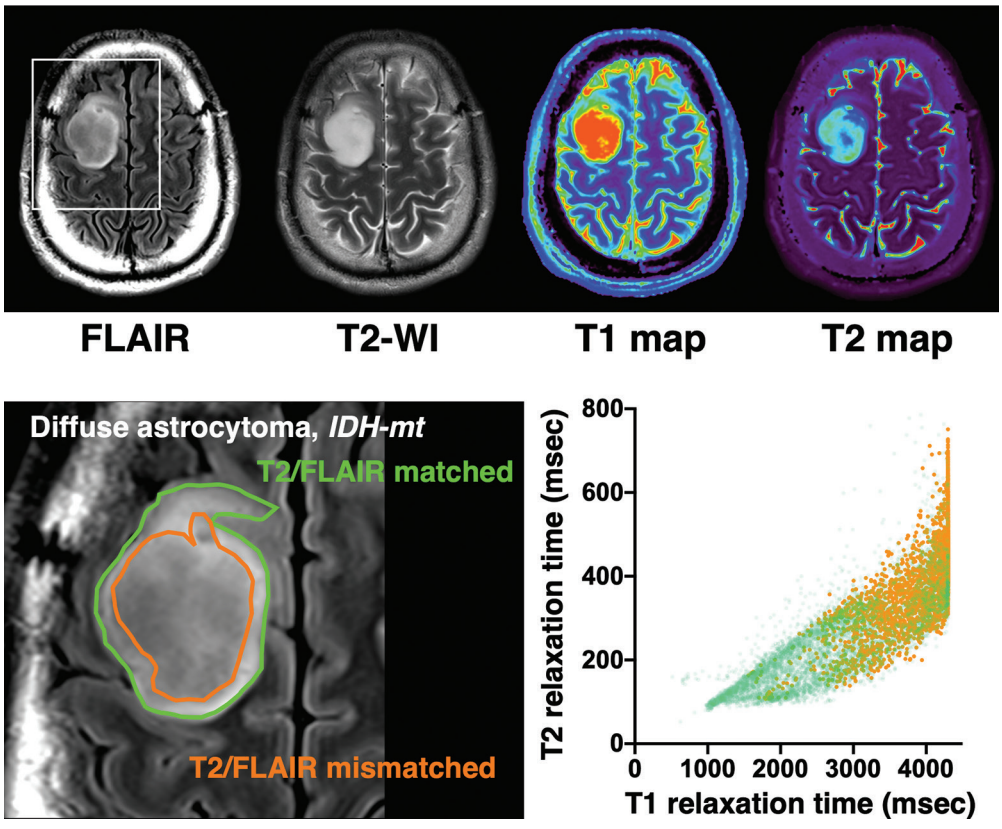

Fig. 1 A representative analysis for an *IDH*-mutant, 1p19q non-codeleted astrocytoma exhibiting a typical "T_2-FLAIR mismatch sign" is presented (Case 1). Two types of VOIs were created, i.e., one encompassing area with matched T_2-FLAIR high-intensity signal (T_2/FLAIR matched) and another with area exhibiting high-T_2 but low-FLAIR intensity signal (T_2/FLAIR mismatched) followed by a scatter plot analysis of T_1- and T_2-relaxation time. Note that data from "T_2/FLAIR mismatched" aggregate at the higher end of the scatter plot. FLAIR, fluid-attenuated inversion recovery; VOI, voxels-of-interest.

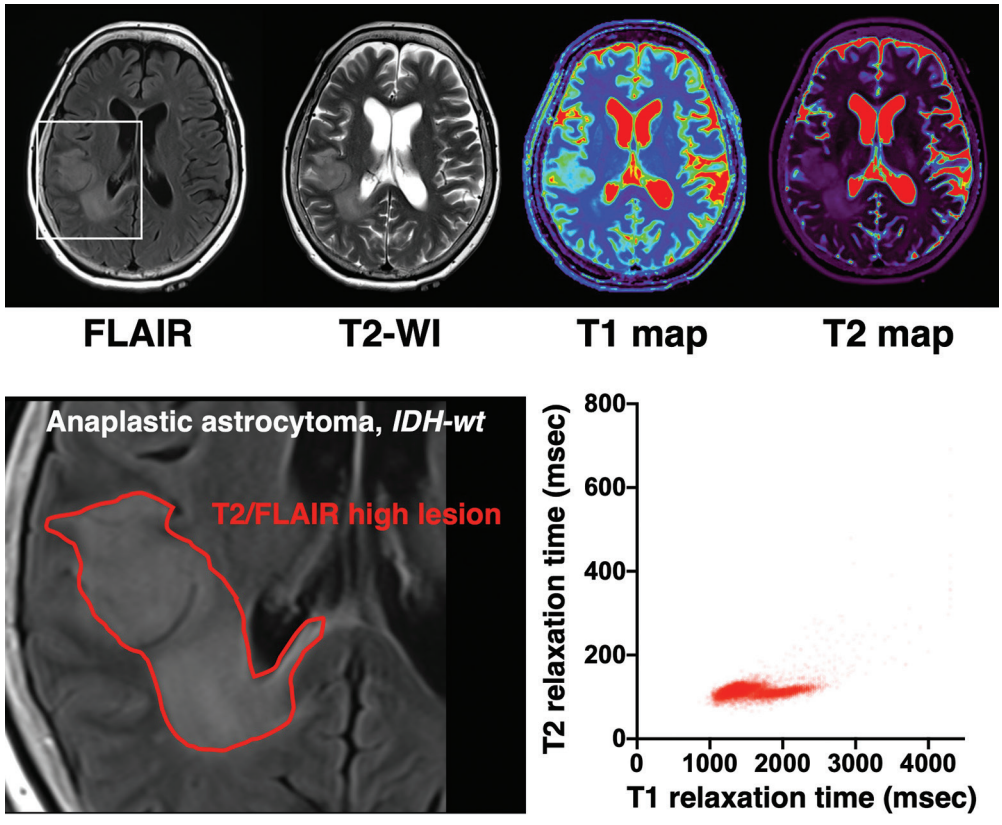

Fig. 2 A representative analysis for an *IDH*-wildtype astrocytoma is presented (Case 8). VOI was created based on high-intensity signals presented on FLAIR, followed by a scatter plot analysis of T_1- and T_2-relaxation time. Note that the scatter plot is more compact and aggregate at the lower end compared with Fig. 1. FLAIR, fluid-attenuated inversion recovery; VOI, voxels-of-interest.

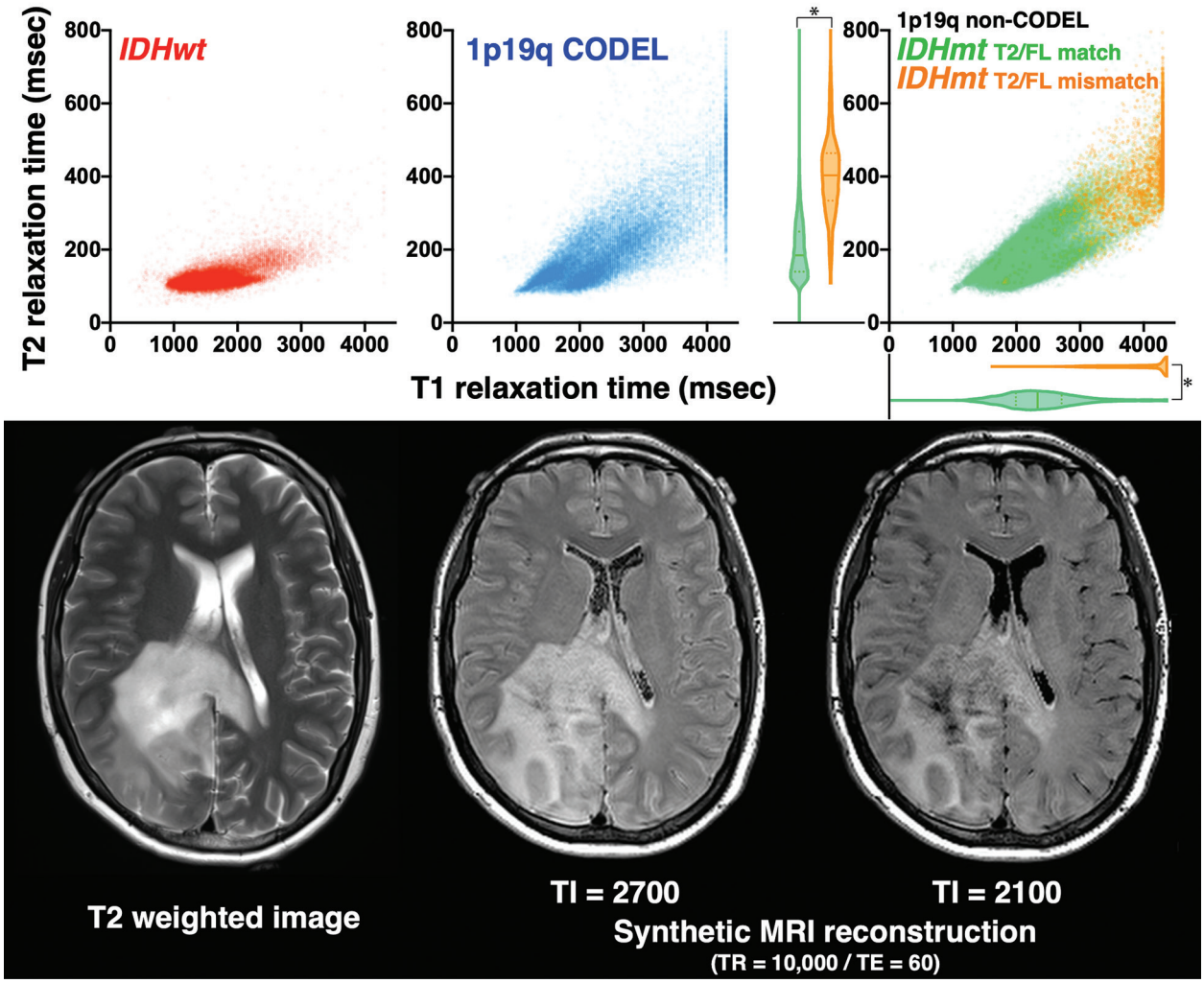

Fig. 3 (Upper row) Scatter plot analysis composed by using all of the data points available in this study is presented. Note that each type of tumor exhibits different data point distribution. T_1-relaxation time was longer in T_2/FLAIR mismatched than in T_2/FLAIR matched region (3895 ± 518 versus 2340 ± 582 ms, means ± SD, unpaired *t*-test, $P < 0.0001$ as shown in asterisk). This phenomenon was also true for T_2-relaxation time (399 ± 106 versus 199 ± 80 ms, means ± SD, unpaired *t*-test, $P < 0.0001$ as shown in asterisk). (Lower row) Synthetic FLAIR images with various inversion time. Although this was an *IDH*-mutant, 1p19q non-codeleted anaplastic astrocytoma, it showed only a small portion of "T_2-FLAIR mismatch", which fails to be categorized as typical "T_2-FLAIR mismatch sign" (Case 2). Note that T_1 = 260 ms is close to T_2WI. Shortening TI improves visualization of T_2-FLAIR mismatch sign. FLAIR, fluid-attenuated inversion recovery.

T_2-FLAIR mismatch (Fig. 3) even with a case of "failed T_2-FLAIR mismatch sign" in *IDH*-mutant, 1p19q non-codeleted tumor. A slight increase in "T_2-FLAIR mismatch region" was also seen in one *IDH*-mutant, 1p19q codeleted tumor (Case 4), which, however, was far from meeting the criteria as recognized as "T_2-FLAIR mismatch sign". Furthermore, an increase in "T_2-FLAIR mismatch region" was not identified in any *IDH*-wildtype tumors.

Discussion

As FLAIR is an MR image acquisition sequence that attempts to suppress signals deriving from cerebrospinal fluid (CSF) by use of inversion recovery, the aimed T_1 value to suppress is typically at around 4000 ms. Likewise, inversion time (TI) was set to 2700 ms in our institution, which relates to 3800 ms in T_1 value for CSF signal suppression under 3T. Figures 1 and 3 clearly show that T_2-FLAIR mismatch sign is a product of signal suppression from the FLAIR sequence. As *IDH*-mutant, 1p19q non-codeleted tumor is the only tumor type among the three that exhibits such a substantially long T_1- and T_2-relaxation time, T_2-FLAIR mismatch sign becomes such a unique and specific image feature of this tumor type. On the other hand, as conventional FLAIR sequence aims to suppress signals from extremely long T_1 values, the sensitivity of discriminating *IDH*-mutant from *IDH*-wildtype tumor is compromised. Our finding suggests that aiming a shorter T_1 value than 4000 ms for the inversion

recovery sequence could contribute to increase this sensitivity. In fact, the validity of this concept is supported by the synthetic MRI reconstructed by shorter TI than usual FLAIR (Fig. 3). Furthermore, Fig. 3 suggests that *IDH*-mutant and *IDH*-wildtype gliomas exhibit distinct T_1/T_2 distribution. Although further study is required, it seems rational to pursue the possibility of directly analyzing T_1/T_2 maps for identifying *IDH* mutations by MRI.

Along with the discussions above, it should also be noted that the presence of T_2-FLAIR mismatch "region" does not necessarily guarantee 1p19q to be non-codeleted. As can be appreciated in Fig. 3, *IDH*-mutant, 1p19q codeleted tumor can also entail some areas that can potentially be recognized as "T_2-FLAIR mismatch region". In fact, the T_2-FLAIR mismatch "sign" was originally proposed as a "complete/near-complete hyperintense signal on T_2WI and relatively hypointense signal on FLAIR except for hyperintense peripheral rim",[2] which functions as a strict diagnostic criterion for identifying *IDH*-mutant, 1p19q non-codeleted tumors. Altering acquisition parameters for FLAIR could compromise the specificity of T_2-FLAIR mismatch sign. Nevertheless, Fig. 3 supports that this modification does not compromise the specificity as to *IDH* mutation status, as shortening TI will have little impact on contaminating *IDH*-wildtype tumors.

In summary, the current study revealed that the T_2-FLAIR mismatch sign is mainly a product of substantially long T_1- and T_2-relaxation time within the tumor. As T_1 effect is affected not only by the tumor itself but also by magnetic field strength, there seems to be significant room to improve imaging parameters to enhance the sensitivity of T_2-FLAIR mismatch sign in LrGG.

Conclusion

This is the first report that investigated the correlation of MR relaxometry and T_2-FLAIR mismatch sign observed in LrGG. The current observation could contribute to further fine-tuning inversion recovery sequence that aims to detect *IDH*-mutant tumors among LrGG tumors.

Acknowledgments

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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