Association analysis of RTEL1 variants with risk of adult gliomas in a Korean population

Suhg Namgoong1, Hyun Sub Cheong2, Jeong-Hyun Kim3, Lyoung Hyo Kim2, Jung Yeon Seo1, Seok-Gu Kang4, Seon-Jin Yoon4,5, Se Hoon Kim6, Jong Hee Chang4*, Hyoung Doo Shin1,7*

1 Department of Life Science, Sogang University, Seoul, Republic of Korea, 2 Department of Genetic Epidemiology, SNP Genetics Inc., Seoul, Republic of Korea, 3 Asan Institute for Life Sciences, University of Ulsan Collage of Medicine, Seoul, Republic of Korea, 4 Department of Neurosurgery, Yonsei University College of Medicine, Seoul, Republic of Korea, 5 Department of Biochemistry and Molecular Biology, College of Medicine, Yonsei University Seoul, Republic of Korea, 6 Department of Pathology, Yonsei University College of Medicine, Seoul, Republic of Korea, 7 Research Institute for Basic Science, Sogang University, Seoul, Republic of Korea

* hdshin@sogang.ac.kr (HDS); CHANGJH@yuhs.ac (JHC).

Abstract

Previous studies have identified multiple loci for inherited susceptibility to glioma development, including the regulator of telomere elongation helicase 1 (RTEL1). However, the association between RTEL1 variants and risk of glioma has not been well understood. Therefore, we sought to comprehensively examine the genetic interaction between RTEL1 variants and risk of glioma with respect to defined histological and molecular subtypes. We employed a case-control study involving 250 adult glioma patients with previous molecular alterations and 375 population–based controls within Korean populations. Statistical analyses on the association between RTEL1 single nucleotide polymorphisms (SNPs) and glioma risk were conducted using unconditional logistic regression. Additional conditional and stepwise analyses were performed on significant RTEL1 SNPs. We detected significant associations (Bonferroni P < .05) between six SNPs (rs6089953, rs3848669, rs6010620, rs3787089, rs6062302, and rs115303435) and risk of glioma in the Korean subjects. The two coding variants, rs6062302 (D664D) and rs115303435 (A1059T), were plausibly causal variants and were independent among the significantly associated RTEL1 variants. The glioma subgroup analyses showed that the causal variants (rs6062302 and rs115303435) may be associated with increased risk of glioma regardless of histological grades and molecular alterations. This study provides a deeper understanding of relationships between RTEL1 variants and risk of glioma. Further studies are required to ascertain the impact of those variants on glioma susceptibility.

Introduction

Glioma is a common tumor which develops within the central nervous system (CNS) [1, 2]. It is derived from of the neuroglial stem and progenitor cells, accounting for 28% of all brain
primary tumors and 80% of malignant brain tumors [2]. With the implementation of 2016 World Health Organization Classification of Tumors of the CNS (2016 CNS WHO), the gliomas of the brain are required to be diagnosed with the isocitrate dehydrogenase \((IDH)\) and the chromosome abnormalities of 1p and 19q status [3]. These genetic alterations have been accepted by worldwide neuro-oncology groups, and most of the glioma patients are being classified into the category of diffuse astrocytoma, anaplastic astrocytoma, oligodendroglioma, anaplastic oligodendroglioma, or glioblastoma (GBM) with the molecular signatures [3–5].

In addition to the integrated phenotypic and genotypic features of glioma, many genetic studies have found that common inherited variants near several genes (\(TERC, TERT, EGFR, CDKN2B, PHLDB1\) and \(RTEL1\)) are associated with increased risk of adult glioma [6]. Genome-wide association studies (GWASs) have found that variants in the regulator of the telomere elongation helicase1 (\(RTEL1\)) gene are associated with increased risk of adult glioma in White populations [7–9]. In case-control studies for glioma, the associations were detected for the intronic SNPs (\(rs6010620\) and \(rs2297440\)) of \(RTEL1\) in the United States (US) [10] and Han Chinese populations [11]. Meta-analyses showed that \(rs6010620\) is associated with increased risk of glioma in populations of both European and Asian descent, although this SNP has an inconclusive effect on glioma risk [12, 13]. In molecular groups of gliomas that have gained the telomerase reverse transcriptase (\(TERT\)) promoter mutation, \(IDH\) mutation, and 1p/19q codeletion, \(rs6010620\) serves as protection against glioma susceptibility in \(TERT\) mutation status [14].

However, association between \(RTEL1\) SNPs, including coding variants, and risk of gliomas is not obvious. Therefore, we analyzed the selected \(RTEL1\) SNPs, including previous glioma variants, for association with risk of adult gliomas in Korean populations. We also examined the possible interactions between susceptibility alleles and glioma subgroups such as grades, histologic features, and molecular information.

Materials and methods

Study subjects

The blood samples of 250 Korean glioma patients were collected at the Yonsei University Severance Hospital and collaborating hospitals, diagnosed between 2006 and 2016. Case subjects were older than 18 years of age and were categorized into glioma subtypes based on histopathological and molecular features according to the 2007 and 2016 WHO classification of CNS tumors [3]. For molecular alterations, \(IDH1\) or \(IDH2\) mutation and 1p/19q codeletion status were observed using previously described methods [15, 16]. The institutional review board of Yonsei University Severance Hospital approved the study protocols and the patients gave written informed consent for participation. As controls, a total of 375 unrelated population-controls (PCs), which excluded participants who had past medical history of various cancer types, were collected from the National Biobank of Korea, the Korean Genome and Epidemiology Study (KoGES) Consortium [17]. The PCs consisted of quality-controlled biospecimen collections from population-based cohorts which comprised 10,038 blood donors aged 40 to 60 years from the Ansung-Ansan Community-based Cohort in 2001. Genomic DNA of blood samples was isolated using the Wizard Genomic DNA Purification Kit (Promega, Madison, WI) for genetic analyses.

SNP selection and genotyping

The candidate \(RTEL1\) SNPs were filtered to remove those sites with minor allele frequency (MAF) <5% in Han Chinese Beijing and Japanese Tokyo panels from the 1000 Genomes Project [18]. The SNPs (\(rs6089953, rs6010620, rs4809324, rs6062302,\) and \(rs3208008\)) were included...
according to previous associations with risk of gliomas [9, 10]. The final 26 SNPs in \textit{RTEL1} were selected on the basis of high linkage disequilibrium (LD) between SNPs of interest ($r^2 > .98$). The glioma SNP rs2297440 was excluded from our study because of perfect LD ($r^2 = 1$) with rs6010620 in East Asian populations [18, 19]. We also included low frequency (MAF \leq 5\%) of seven non-synonymous SNPs (rs184051277, rs199685200, rs77086616, rs199796539, rs20093423, rs115303435, and rs115264605), except that non-synonymous SNPs were not designable on Fluidigm SNP Type assays (Fluidigm Corp., South San Francisco, CA, US). In addition, all loci were genotyped by the Fluidigm high-throughput platform and Fluidigm EP1 SNP Genotyping 192.24 Dynamic Array. The discrete genotype data were analyzed with the BioMark SNP Genotyping analysis software (version 4.3.2). Among 26 \textit{RTEL1} SNPs, four SNPs (rs184051277, rs199685200, rs199796539, and rs115264605) were monomorphic and excluded from additional statistical analysis.

**Statistics**

For each SNPs, the deviation of the genotype proportions from those expected under Hardy-Weinberg equilibrium (HWE) was examined. LD analysis between genotyped SNPs was carried out using the Haploviev v4.2 software from the Broad Institute (http://www.broadinstitute.org/mpg/haploviev). Haplotypes of each individual were reconstructed using the PHASE 2.1 software [20]. Odds ratios (ORs) and corresponding $P$-values were calculated using unconditional logistic regression under an additive model, adjusted for age and sex as covariates. The significant $P$-values were corrected for multiple testing of 22 times using Bonferroni correction. In addition, conditional logistic regression and stepwise analysis were undertaken to identify the independence of association among the significant \textit{RTEL1} variants. All statistical analyses were conducted using SAS 9.4 software (SAS Inc., Cary, NC, US).

**Functional analysis**

To predict the function of significantly associated \textit{RTEL1} SNPs with risk of glioma, \textit{in silico} analysis for non-synonymous SNPs was performed using TransFIC (http://bbglab.irbbarcelona.org/transfic/home), which includes well-known tools (SIFT, Polyphen2, MutationAssessor) for assessing the impact of variants in cancer. The TransFIC method normalizes the results from the tools on a baseline tolerance of missense SNPs with dissimilar functions. FuncPred (https://snpinfo.niehs.nih.gov/snpinfo/snpfunc.html) was used to identify the transcriptional regulation of significant \textit{RTEL1} SNPs.

**Results**

**Subjects characteristics**

All glioma patients composed of astrocytic and oligodendroglial tumor groups fulfilled the inclusion criteria defined by the 2007 WHO classification [21]. The majority of gliomas (92\%) which included test results of \textit{IDH} mutation and 1p/19q codeletion status were categorized as astrocytomas, oligodendrogliomas, and GBM as defined by the 2016 CNS WHO classification [3]. The \textit{IDH}-mutants were found in 72 (29.6\%) of the 243 glioma patients and the rate of glioma patients with 1p/19q codeletion was 25.9\% (61 of 236). Molecular alterations in GBM were less prevalent in both \textit{IDH} mutants (10.9\%) and 1p/19q codeletions (11.6\%). The case group consisted of patients with 250 unrelated adult gliomas (mean age 51.13 ± 14.71, 52.4\% male) and the control group consisted of 375 individuals over 40 years old (mean age 53.61 ± 8.97, 46.9\% male). The detailed histologic and acquired molecular features of cases are summarized.
in Table 1. In addition, we compare molecular characteristics of obtained IDH mutations and 1p/19q codeletions with other glioma studies (S1 Table).

Genotyping results and associations between RTEL1 SNPs and glioma risk

The genotyped SNPs’ location of RTEL1 is displayed in S1A Fig. Three LD blocks were constructed from the 22 RTEL1 SNPs (S1B and S2 Figs). We found that the four sets of SNPs (rs6089953-rs3848669, rs6010620-rs3787089, rs62207047-rs4809324, and rs3208008-rs2297441) had high LD ($r^2$ > .90). Although the genotype distributions for SNPs were in accordance with HWE ($P > .05$), a novel missense variant (rs77086616, T434M) in RTEL1 was only observed in anaplastic astrocytoma and GBM patients (HWE $P = 1.55 \times 10^{-16}$). In addition, 13 RTEL1 SNPs were found to have significant associations with risk of adult gliomas in Korean populations (Table 2). After applying the of Bonferroni correction (threshold $P = .0023$), four intronic (rs6062302, rs115303435), one synonymous (rs6062302, D664D), and one missense (rs115303435, A1059T) SNP were found to be significant for glioma risk.

Genetic effects of causal variants on glioma risk

To further confirm the independent association between significant SNPs and glioma risk, stepwise and conditional logistic regression analyses were conducted on the six significant RTEL1 variants. As shown in Table 3, two SNPs (rs6062302 and rs115303435) remained in the model at the parametric discriminant $P$-value (0.05). After applying conditional logistic regression, the same conclusion was independently reached, although rs6062302 showed a much weaker association than rs115303435 after the significant RTEL1 variants were conditioned. In addition, we examined the differential association between the two independent SNPs (rs6062302 and rs115303435) and glioma subgroups with respect to clinical characteristics such as WHO grade, histological type, and molecular alteration. They were found to be possibly involved with increased risk of gliomas regardless of histologic features, IDH mutations, and 1p/19q codeletion status (Fig 1).

Assessment of the functional effects of RTEL1 variants

Our significant missense variants were evaluated via in silico analysis using the TransFIC method. Although rs115303435 (A1059T) had low functional and structural impact on the cancer data, rs77086616 (T434M) was observed to have medium functional impact on RTEL1 when the TransFIC method was applied with the SIFT tool. In the FuncPred method, a coding variant rs6062302 (D664D) was predicted to alter transcription factor binding (S2 Table).
Table 2. Genotyped RTEL1 SNP information and associations of variants with risk of glioma.

| SNP (allele) | Chr. position (GRCh38.p7) | SNP location | Minor allele frequency | HWE P | OR (95% CI) | P   | pcorr |
|--------------|---------------------------|--------------|------------------------|-------|-------------|-----|-------|
| rs6089759 T>G | 6365966 | Promoter | .166 | .115 | .135 | .388 | .586 | .885 | 1.61 (1.15–2.25) | .005 NS |
| rs1220222 C>A | 6365824 | 5'UTR | .078 | .076 | .077 | .647 | .111 | .130 | 1.02 (0.65–1.58) | .93 NS |
| rs2297432 C>T | 63659310 | 5'UTR | .150 | .124 | .134 | .852 | .557 | .556 | 1.25 (0.90–1.74) | .17 NS |
| rs6089953 A>G | 63659655 | Intron 2 | .316 | .240 | .270 | .386 | .497 | .951 | 1.52 (1.17–1.97) | .001 .03 |
| rs2738778 C>T | 6366047 | 5'UTR | .454 | .493 | .478 | .008 | .500 | .233 | 0.82 (0.66–1.04) | .10 NS |
| rs35902944 G>C | 6367704 | Intron 10 | .365 | .324 | .340 | .415 | .786 | .710 | 1.19 (0.93–1.51) | .15 NS |
| rs6010620 A>G | 6367848 | Intron 11 | .320 | .241 | .273 | .642 | .964 | .918 | 1.55 (1.19–2.01) | .0009 .02 |
| rs62207047 C>T | 6367961 | 5'UTR | .126 | .081 | .099 | .578 | .628 | .983 | 1.77 (1.20–2.59) | .003 NS |
| rs77086616 C>T | 6368582 | Exon 15 (T434M) | .012 | .000 | .005 | 2.71x10^-7 | 1.55x10^-16 | - | - | .01 |
| rs4809324 A>C | 6368686 | Intron 15 | .127 | .081 | .099 | .572 | .720 | .943 | 1.72 (1.17–2.51) | .005 NS |
| rs9710206 C>T | 6368957 | 5'UTR | .100 | .101 | .101 | .702 | .223 | .234 | 1.01 (0.69–1.47) | .94 NS |
| rs6062302 A>G | 6369444 | Exon 22 (D664D) | .349 | .253 | .290 | .787 | .561 | .621 | 1.62 (1.26–2.10) | .0002 .004 |
| rs6062302 A>G | 6369444 | Exon 22 (D664D) | .349 | .253 | .290 | .787 | .561 | .621 | 1.62 (1.26–2.10) | .0002 .004 |
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| rs77086616 C>T | 6368582 | Exon 15 (T434M) | .012 | .000 | .005 | 2.71x10^-7 | 1.55x10^-16 | - | - | .01 |
| rs4809324 A>C | 6368686 | Intron 15 | .127 | .081 | .099 | .572 | .720 | .943 | 1.72 (1.17–2.51) | .005 NS |
| rs9710206 C>T | 6368957 | 5'UTR | .100 | .101 | .101 | .702 | .223 | .234 | 1.01 (0.69–1.47) | .94 NS |
| rs6062302 A>G | 6369444 | Exon 22 (D664D) | .349 | .253 | .290 | .787 | .561 | .621 | 1.62 (1.26–2.10) | .0002 .004 |
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| rs77086616 C>T | 6368582 | Exon 15 (T434M) | .012 | .000 | .005 | 2.71x10^-7 | 1.55x10^-16 | - | - | .01 |

Logistic regression analysis under additive model was used for calculating ORs and corresponding P-values for SNPs controlling age and sex as covariates. Significant associations are shown in bold face.

aSNPs were analyzed in previous studies on glioma risk.
bBonferroni-adjusted P-values by 22 SNP tests.
cThe P-value was determined using the χ² test because no variants were observed in PCs.

Abbreviation: Chr., chromosome; PC, population control; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; CI, confidence interval; NS, not significant.

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Table 3. Independent association signals among glioma-associated RTEL1 variants.

| SNP         | P     | Stepwise P* | Conditional P-value |
|-------------|-------|-------------|---------------------|
|             | rs6089953b |     | rs3848669 |
| rs6089953b | .001  | -           | .93                 |
| rs3848669  | .0009 | -           | .93                 |
| rs6010620b | .0009 | -           | .93                 |
| rs3787089  | .0002 | .0004       | .05                 |
| rs6062302b | .0002 | .01         | .006                |

The P-values were obtained by logistic analysis between glioma patients (n = 250) and PCs (n = 375) under additive model. Significant associations are shown in bold face.
aThe significance level was set at 0.05 in stepwise selection of glioma-associated RTEL1 SNPs.
bPreviously identified loci in RTEL1.

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Discussion

This study demonstrates that previously identified loci in RTEL1 are confirmed to have an association with increased risk of adult gliomas. Moreover, two coding variants (rs6062302 and rs115303435) were found to confer independent risk for glioma in RTEL1. A novel missense SNP (rs77086616, T434M) was also observed only in Korean glioma samples. In addition, we compared the associations between causal RTEL1 markers and glioma subgroups based on grades of malignancy and histopathological subtypes.

A number of GWASs and candidate gene studies have identified RTEL1 variants involved with genetic predispositions to glioma development [6, 7, 22]. A summary of studies between RTEL1 variants and glioma risk is listed in S3 Table. Of the extensively investigated RTEL1 SNPs, the intronic rs6010620 was the most studied SNP in White and Chinese populations, although there were differences in the effect of this SNP on glioma risk [12]. Recently, the GWAS meta-analyses in up to 30,686 individuals showed that the significant association at RTEL1 rs2297440 was observed between the risk of GBM and non-GBM tumors [7]. However, we did not find any association of the RTEL1 variants from the case-only analysis (rs2297440 was replaced by rs6010620 with LD in East Asian populations).

In case-control studies, rs6010620 and rs2297440 were found to be associated with glioma development [11] and GBM risk [23] in Han Chinese populations. The intronic rs6010620 and rs4809324 were independent predictors of glioma risk in European ancestry individuals [9], whereas the risk of glioma development [11] and GBM [23] in Han Chinese was not influenced by rs4809324. rs6010620, rs2297440, and rs4809324 were presented in one haplotype block which was associated with increased risk of astrocytoma in Chinese populations [24]. Unconditional logistic regression analysis showed that rs6010620 and rs4809324 were associated with increased risk of adult glioma in Korean populations (Table 2). The resulting LD between rs6010620 and rs4809324 was high ($r^2 = .94$, S2 Fig).
In addition to intronic SNPs, the associations between the coding variants (rs6062302 and rs3208008) and risk of adult gliomas were observed in US population study [10], a fact which was replicated in this study (S3 Table). An exome-wide association study has also identified a number of missense SNPs in RTEL1, including rs3208008 (Q1042H) and rs115303435 (A1059T), in a Han Chinese population, although rs115303435 showed marginal association with GBM risk after conditional analysis by rs6010620 (P = .059) [25]. Among those glioma-associated SNPs, rs6062302 and rs115303435 were replicated in our Korean subjects as causal SNPs associated with increased risk of adult gliomas (Table 3). In addition, the new glioma-specific variant (rs77086616, T434M) was identified only in certain cases and was found to be rare (MAF = .005) in this study. More than half of the low-frequency missense alleles were found to have deleterious effects with respect to the intensity of selective pressure among disease alleles [26]. Although rs115303435 and rs77086616 were only observed in this study and in East Asian populations [18], to date, little information has been confirmed between a population-specific variant and glioma risk.

Human RTEL1 is an essential DNA helicase which helps maintain genome stability through telomere maintenance and DNA repair [27]. However, few functional studies on RTEL1 with respect to glioma tumorigenesis have been conducted [22]. As such, it is difficult to assess the role of oncogenic or tumor suppressor pathways. Using in silico analysis, the splicing effect of rs6062302 was studied (S2 Table). A rare variant (rs77086616, T434M) was found to have a medium impact on the RTEL1 function when the TransFIC method was applied. In addition, to identify the significant SNPs that alter the expression level of RTEL1 in brain tissues, we searched for expression quantitative trait locus data (eQTL) from the UK Brain Expression Consosium (Braineac; http://www.braineac.org). Healthy individuals of Western European descent with the rs6062302 C>T allele showed increased mRNA expression levels in the temporal and frontal cortex compared to other brain regions. However, rs77086616 and rs115303435 data were not available in the public eQTL database.

Recent advances in molecular profiling have contributed to understanding the molecular aberrations of diffuse gliomas in adults [28]. IDH mutations, most of the R132 codon of IDH1, are found frequently in a majority of astrocytomas and oligodendrogliomas cases [16]. The combined chromosome imbalances of 1p and 19q resulting in loss of heterozygosity are prognostic biomarkers for oligodendrogial tumors [15]. Likewise, our oligodendroglomas were shared in almost all cases with both IDH mutations and 1p/19q codeletion (Table 1). Among the associated inherited risk variants, RTEL1 variants were found to be associated with risk of glioma regardless of molecular alterations [6, 14]. The similar pattern was observed for our causal variants with glioma, stratified by 2016 CNS WHO, morphology, IDH mutations, and 1p/19q codeletion (Fig 1). In particular, rs6062302 and rs115303435 were more significantly associated with IDH-wildtype gliomas than with IDH mutants. The ORs of rs115303435 were higher than rs6062302 in all glioma classes. However, the subgroup analyses were limited in their statistical power due to small number of cases analyzed; these results should be interpreted with caution. In addition, we used general PCs matched for age and sex to estimate the impact of the association between RTEL1 variants and risk of adult gliomas. Although population-based controls lack clinical information for detailed inclusion and exclusion criteria, the use of PCs in this study may be considered as an alternative method for assessing genetic effects [29].

Despite these limitations, the present study reinforces understanding of RTEL1 association with adult gliomas in Korean populations. Future studies considering our findings in larger glioma samples with molecular alterations must test the reproducible markers for understanding of glioma pathogenesis.
Supporting information

S1 Table. Comparisons of IDH mutations and 1p/19q co-deletion status in each study group. Abbreviation: US indicates United States; GBM, glioblastoma.

(DOCX)

S2 Table. In silico analysis of RTEL1 rs6062302 (D664D). In silico analysis was conducted using FuncPred (https://snpinfo.niehs.nih.gov/snpinfo/snpfunc.html). Lowercase alleles in motif (forward strand) indicate the rs6062302 position. Threshold score for associated splicing factor SF2/ASF was 1.956. Abbreviation: ESE, exonic splicing enhancer; ESS, exonic splicing silencer.

(DOCX)

S3 Table. The Studies between RTEL1 variants and glioma risk. Significant associations are shown in bold face. Abbreviation: OR (95% CI), odds ratio (95% confidence interval); NA, not available. *Causal SNPs on glioma risk in present study ⁹Protective allele

(DOCX)

S1 Fig. The gene map of RTEL1 (NM_032957.4) on chromosome 20q13.33 (38.444 kb). (A) A map of RTEL1. Coding exons are marked by black blocks, and 5’- and 3’-untranslated regions by white blocks. (B) Haplotypes of RTEL1. The BL1 ht4 (OR = 1.67, P = .003), BL2 ht1 (OR = 0.70, P = .003), BL2 ht4 (OR = 1.86, P = .002), BL3 ht1 (OR = 1.40, P = .007), and BL3 ht2 (OR = 1.67, P = .03) were associated with risk of adult gliomas. Abbreviation: ht, haplotype; PC, population control.

(TIF)

S2 Fig. The LD structure of genotyped RTEL1 SNPs. The region includes three LD blocks marked by triangles with black lines. The SNPs in the haplotype blocks are shown in bold. Numbers and grayscale shades in boxes indicate $r^2$ values.

(TIF)

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Author Contributions

Conceptualization: Suhg Namgoong, Jeong-Hyun Kim, Hyoung Doo Shin.

Data curation: Hyun Sub Cheong, Lyoung Hyo Kim.

Formal analysis: Suhg Namgoong, Jung Yeon Seo.

Funding acquisition: Jeong-Hyun Kim, Hyoung Doo Shin.

Investigation: Suhg Namgoong, Jung Yeon Seo.

Methodology: Hyun Sub Cheong, Lyoung Hyo Kim.

Project administration: Jeong-Hyun Kim, Hyoung Doo Shin.

Resources: Seok-Gu Kang, Seon-Jin Yoon, Se Hoon Kim, Jong Hee Chang.

Software: Suhg Namgoong, Hyun Sub Cheong.

Supervision: Jong Hee Chang, Hyoung Doo Shin.
Validation: Hyun Sub Cheong, Jeong-Hyun Kim.
Visualization: Suhg Namgoong.
Writing – original draft: Suhg Namgoong.
Writing – review & editing: Seon-Jin Yoon, Jong Hee Chang, Hyoung Doo Shin.

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