MR Imaging Correlates for Molecular and Mutational Analyses in Children with Diffuse Intrinsic Pontine Glioma


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ABSTRACT

BACKGROUND AND PURPOSE: Recent advances in molecular techniques have characterized distinct subtypes of diffuse intrinsic pontine gliomas. Our aim was the identification of MR imaging correlates of these subtypes.

MATERIALS AND METHODS: Initial MRIs from subjects with diffuse intrinsic pontine gliomas recruited for a prospective clinical trial before treatment were analyzed. Retrospective imaging analyses included FLAIR/T2 tumor volume, tumor volume enhancing, the presence of cyst and/or necrosis, median, mean, mode, skewness, kurtosis of ADC tumor volume based on FLAIR, and enhancement at baseline. Molecular subgroups based on EGFR and MGMT mutations were established. Histone mutations were also determined (H3F3A, HIST1H3B, HIST1H3C). Univariate Cox proportional hazards regression was used to test the association of imaging predictors with overall and progression-free survival. Wilcoxon rank sum, Kruskal-Wallis, and Fisher exact tests were used to compare imaging measures among groups.

RESULTS: Fifty patients had biopsy and MR imaging. The median age at trial registration was 6 years (range, 3.3–17.5 years); 52% were female. On the basis of immunohistochemical results, 48 patients were assigned to 1 of 4 subgroups: 28 in MGMT−/epidermal growth factor receptor (EGFR)−, 14 in MGMT−/EGFR+, 3 in MGMT+/EGFR−, and 3 in MGMT+/EGFR+. Twenty-three patients had histone mutations in H3F3A, 8 in HIST1H3B, and 3 in HIST1H3C. Enhancing tumor volume was near-significantly different across molecular subgroups (P = .04), after accounting for the false discovery rate. Tumor volume enhancing, median, mode, skewness, and kurtosis ADC T2-FLAIR/T2 were significantly different between patients with H3F3A and HIST1H3B/C mutations.

CONCLUSIONS: MR imaging features including enhancement and ADC histogram parameters are correlated with molecular subgroups and mutations in children with diffuse intrinsic pontine gliomas.

ABBREVIATIONS: DIPG = diffuse intrinsic pontine glioma; EGFR = epidermal growth factor receptor; FDR = false discovery rate; PFS = progression-free survival; PG = postgadolinium; OS = overall survival

Diffuse intrinsic pontine glioma (DIPG) is a malignant brain tumor that accounts for 75%–80% of brain stem tumors in children.1 Despite medical therapy, these tumors have a poor prognosis, with a median survival at 1, 2, and 3 years of 41%, 15.3%, and 7.2%, respectively.2 The 2016 World Health Organization classification of brain tumors introduced the term “diffuse midline glioma, H3 K27M mutant” to describe these neoplasms due to the high prevalence of unique histone protein mutations that differ from those of supratentorial (hemispheric) pediatric high-grade gliomas and adult high-grade gliomas. While H3 K27M is the most common variant detected, more recently, other distinct histone mutations have been identified in DIPG, which appear to correspond to subgroups with
different prognosis and pathologic phenotypes. Identification of these subgroups of tumors is important to appropriately counsel families and tailor treatment strategies.

Radiogenomic techniques are emerging as valuable tools to noninvasively characterize brain tumors and are increasingly important, given the evolving molecular landscape in pediatric neuro-oncology. Although most data available to date pertain to adult high-grade gliomas, radiogenomic techniques have been successfully implemented to characterize atypical teratoid/rhabdoid tumors and medulloblastomas. A challenge to molecular analysis of DIPGs is that historically, patients with these tumors did not routinely undergo biopsy due to a perceived high likelihood of morbidity associated with the procedure; consequently, most imaging-based studies do not have pathologic or molecular correlates. Despite this limitation, important imaging-based prognostic factors have been described for DIPG. Jansen et al and Hoffman et al reported that ring enhancement was associated with shorter survival. Chen et al reported worse outcome in DIPGs with lower ADC values at baseline. Poussaint et al reported that lower diffusion values on ADC histogram analysis, high skewness, and enhancement were associated with shorter survival. The association among these MR imaging features, the molecular subgroups, and various histone mutations has not been elucidated.

The purpose of this study was to investigate the relationship between the molecular subgroup and histone mutations of DIPGs and MR imaging features on anatomic sequences, and ADC histogram analysis, using the baseline MR imaging from a prospective clinical trial of children with newly diagnosed DIPG who underwent biopsy.

**MATERIALS AND METHODS**

**Subjects**

Patients for this study were recruited as part of an institutional review board (Dana Farber Cancer Institute)-approved, Health Insurance Portability and Accountability Act–compliant, multicenter clinical trial: Molecularly Determined Treatment of Diffuse Intrinsic Pontine Gliomas (DIPG) (NCT01182350). Prospective subjects had MR imaging that showed classic clinical-imaging criteria of nonmetastatic DIPG, including an expansile and infiltrative T1-isointense or -hypointense and T2-FLAIR and T2-hyperintense mass centered within the pons, encompassing at least 50% of the pons with no or little contrast enhancement, which could vary. Findings on clinical examination included multiple cranial nerve neuropathies, long tract signs, and ataxia. Detailed criteria for inclusion and exclusion are summarized in On-line Table 1. The patients enrolled in the trial underwent a biopsy before initiation of therapy; the biopsy target and approach were at the discretion of the neurosurgeon, with the goal of minimizing operative risk. All subjects received local radiation therapy (59.4 Gy) with adjuvant bevacizumab, as per the standard of care. Subsequently, patients were stratified into different treatment arms with erlotinib and/or temozolomide at the start of radiation therapy based on MGMT promoter methylation status and epidermal growth factor receptor (EGFR) expression in tumor tissue obtained from surgical biopsies.

Of 53 patients enrolled, 50 underwent biopsy and were included in the analytic cohort of this study. Subjects without biopsy were excluded from this analysis. We performed a retrospective review that included biopsy data (histone mutations, molecular groups), MR imaging features on baseline MR imaging, and clinical outcomes. The molecular analysis determined the MGMT methylation status and expression of EGFR; 4 categories were derived from molecular analysis: MGMT-/-EGFR, MGMT-/-EGFR+, MGMT+/EGFR, MGMT+/EGFR+. Three histone mutations were identified through whole-genome RNA sequencing: H3F3A, HIST1H3B, and HIST1H3C. Clinical end points of the study were determined with longitudinal follow-up. Overall survival (OS) was measured from the time of registration to death or to last follow-up if censored. Progression-free survival (PFS) was measured from the time of registration to progression or death (whichever was first) or to the last follow-up if censored.

**Image Analysis**

The MR imaging of the brain used for analysis corresponded to the baseline examination obtained before treatment and biopsy. Images were obtained using 3T (n = 17) and 1.5T (n = 33) scanners. A standard clinical protocol was used, which included the following: sagittal T1, axial T2, precontrast axial T2-FLAIR, axial DTI (TR = 6500 ms, TE = 88 ms, section thickness = 2 mm, b-values = 0 and 1000 s/mm², 30 gradient directions), and postgadolinium (PG) 3D T1.

Volumetric data of various components of the tumor were obtained by generating 3D ROIs on a Vitrea workstation (Vital Images) on the anatomic sequences. Specifically, T2-FLAIR/T2 volume represents the volume of tissue (milliliter) with abnormal T2 hyperintense signal on a 2D TSE T2-FLAIR sequence; for cases in which T2-FLAIR was unavailable, this parameter was estimated using a 2D T2 TSE sequence. Tumor volume enhancing represents the volume (milliliter) of enhancement within the tumor estimated on the PG 3D T1 sequence.

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**Table 1: Baseline patient characteristics (n = 50)**

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>No. (%) or Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of MR imaging studies</td>
<td>50 (100)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 24 (48) Female 26 (52)</td>
</tr>
<tr>
<td>Median age at registration (range) (yr)</td>
<td>6 (3.3–17.5)</td>
</tr>
<tr>
<td>Unassigned</td>
<td>2</td>
</tr>
<tr>
<td>Mutational status*</td>
<td>Any histone mutation 34/49 (69) Wild-type 15/49 (31)</td>
</tr>
<tr>
<td>Histone mutation (among patients with any histone mutations)*</td>
<td>H3F3A 23/34 (68) HIST1H3B 8/34 (24) HIST1H3C 3/34 (9) Median follow-up time (range) (mo) 10.9 (0.4–33.4)</td>
</tr>
</tbody>
</table>

*One patient with both H3F3A and HIST1H3B histone mutations was excluded.

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To perform ADC histogram analysis, we registered the ADC maps to the anatomic sequence of interest (T2-FLAIR/T2 and PG T1) using tools from the FSL library (http://www.fmrib.ox.ac.uk/fsl), as described by Poussaint et al. Briefly, we transformed the $b=0$ (and subsequently the ADC map) into the space of the individual anatomic sequences. Subsequently, 3D ROIs were created using the thresholding feature in Fiji (http://fiji.sc/), an Open Source (https://opensource.org/) distribution of Java modules along with ImageJ software (National Institutes of Health); we then extracted the values from every pixel from the ADC map within the corresponding ROI.

We applied a uniform threshold to the ADC maps, ranging from 600 to $2600 \times 10^{-6}$ mm$^2$/s to differentiate solid tumor from cyst/necrosis. ADC histograms were then generated using a uniform bin width of 10 mm$^2$/s. Histogram metrics used for statistical analysis were mean, median, mode, skewness, and kurtosis of these histograms.

**Statistical Analysis**

Clinical and demographic variables were summarized using descriptive statistics. Continuous measures were summarized using medians and ranges, and categoric measures were summarized
using frequencies and proportions. Kaplan-Meier curves were used to summarize OS and PFS for all patients. Univariate Cox proportional hazards regression was used to test the association of imaging predictors with OS and PFS. The Wilcoxon rank sum and Kruskal-Wallis tests were used to compare continuous imaging features among groups. The Fisher exact test was used to compare categoric imaging features among groups. When applicable, the presence of enhancement (defined as patients with tumor volume enhancing >0 mL) was recorded as a binary measure and used for subanalyses. Due to the low number of H3.1 mutations (HIST1H3B = 8, HIST1H3C = 3), we grouped them into a single category and compared them with H3F3A mutations. For each outcome tested, we calculated the false discovery rate (FDR) using the Benjamani-Hochberg method to account for multiple hypothesis tests. Tests with a calculated FDR of \( P \leq 0.1 \) were considered statistically significant after FDR adjustment.\(^{17}\) R version 3.5.0 (http://www.r-project.org) and SAS version 9.4 (SAS Institute) were used for statistical analyses.

RESULTS

Patients

Of the 50 patients who underwent biopsy, all had baseline MR imaging studies. The median age at time of enrollment was 6 years (range, 3.3–17.5 years). Twenty-six (52%) subjects were female, 48 (96%) were successfully assigned to a molecular subgroup (2 unassigned), and 34 (68%) patients had (single) identifiable histone mutations (Table 1). One subject was excluded from subsequent analysis due to the concurrent presence of 2 histone mutations.

Tumor Enhancement and Survival

The presence of enhancement (hazard ratio = 3.2; 95% CI, 1.5–7.0; \( P = 0.003 \)) was associated with decreased OS after FDR adjustment (On-line Fig A and On-line Table 2). OS was not associated (\( P = 0.07 \)) with T2-FLAIR/T2 volume, tumor volume cyst/necrosis, the presence of necrosis, tumor volume enhancing (subset of patients with enhancing tumor of >0 mL), ADC_FLAIR histogram metrics, or PG ADC enhancement histogram metrics after FDR adjustment.

Higher tumor volume enhancing (\( P = 0.02 \)) and the presence of enhancement (\( P = 0.06 \)) showed a strong trend with decreased PFS but were not significant after FDR adjustment (On-line Fig B and On-line Table 2). T2-FLAIR/T2 tumor volume (\( P = 0.07 \)) also showed a trend toward a significant association with decreased PFS.

Molecular Subgroup Analysis

There were differences in tumor volume enhancing across the 4 molecular subgroups within the subset of patients with tumor volume enhancing of >0 mL, but the test was not significant.
Table 2: Association of imaging predictors and variant histone mutation (H3F3A versus HIST1H3B/C) (n = 34)

<table>
<thead>
<tr>
<th>Imaging Parameters (Median) (Range)</th>
<th>No.</th>
<th>H3F3A (n = 23)</th>
<th>HIST1H3B and HIST1H3C (n = 11)</th>
<th>Wilcoxon P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLAIR/T2 tumor volume</td>
<td>33</td>
<td>35.1 (10.7–70.9)</td>
<td>40.3 (11.6–63)</td>
<td>.4</td>
</tr>
<tr>
<td>Tumor volume cyst/necrosis (mL) in patients</td>
<td>16</td>
<td>0.8 (0.07–8.1)</td>
<td>2.1 (0.09–4.1)</td>
<td>.8</td>
</tr>
<tr>
<td>Presence of necrosis (yes vs no) in patients</td>
<td>22</td>
<td>11/16 (69%)</td>
<td>5/6 (83%)</td>
<td>.6</td>
</tr>
<tr>
<td>Tumor volume enhancing (mL) in patients</td>
<td>22</td>
<td>2.5 (0.08–12.4)</td>
<td>6.3 (3.6–15.2)</td>
<td>.04</td>
</tr>
<tr>
<td>Presence of enhancement (yes vs no)</td>
<td>31</td>
<td>16/21 (76%)</td>
<td>6/10 (60%)</td>
<td>.4</td>
</tr>
<tr>
<td>Mean ADC FLAIR $\times 10^{-6}$ mm$^2$/s</td>
<td>31</td>
<td>1306 (893.9–1915.2)</td>
<td>1370 (1189.4–2146.0)</td>
<td>.03</td>
</tr>
<tr>
<td>Median ADC FLAIR $\times 10^{-6}$ mm$^2$/s</td>
<td>31</td>
<td>1260 (906.7–1913)</td>
<td>1391 (1150.8–2214.4)</td>
<td>.02</td>
</tr>
<tr>
<td>Mode ADC FLAIR $\times 10^{-6}$ mm$^2$/s</td>
<td>31</td>
<td>1257 (895.5–1886.4)</td>
<td>1316 (1150.8–2214.4)</td>
<td>.009</td>
</tr>
<tr>
<td>Skewness ADC FLAIR</td>
<td>29</td>
<td>1 (0.6–2.0)</td>
<td>0.03 (1–3–0.9)</td>
<td>.03</td>
</tr>
<tr>
<td>Kurtosis ADC FLAIR</td>
<td>29</td>
<td>1.8 (0.3–8.2)</td>
<td>1.3 (1–11.2–4)</td>
<td></td>
</tr>
</tbody>
</table>

* Fisher exact test P value.
* Test is significant after FDR adjustment <.1.

Table 3: Association of imaging predictors with mutational status (any histone mutation versus wild-type) (n = 49)

<table>
<thead>
<tr>
<th>Imaging Parameters (Median) (Range)</th>
<th>No.</th>
<th>Any Histone Mutation (n = 34)</th>
<th>Wild-Type (n = 15)</th>
<th>Wilcoxon P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ADC T2-FLAIR/T2 $\times 10^{-6}$ mm$^2$/s</td>
<td>45</td>
<td>1360 (895.9–2098.3)</td>
<td>1127 (1040.4–1838.5)</td>
<td>.9</td>
</tr>
<tr>
<td>Median ADC T2-FLAIR/T2 $\times 10^{-6}$ mm$^2$/s</td>
<td>45</td>
<td>1309 (906.7–2146.0)</td>
<td>1316 (952.0–1925.7)</td>
<td>.9</td>
</tr>
<tr>
<td>Mode ADC T2-FLAIR/T2 $\times 10^{-6}$ mm$^2$/s</td>
<td>45</td>
<td>1311 (895.5–2214.4)</td>
<td>1342 (893.8–1965.4)</td>
<td>.99</td>
</tr>
<tr>
<td>Skewness ADC T2-FLAIR/T2</td>
<td>42</td>
<td>0.5 (1–3–2.0)</td>
<td>0.8 (0–9–2.8)</td>
<td>.4</td>
</tr>
<tr>
<td>Kurtosis ADC T2-FLAIR/T2</td>
<td>42</td>
<td>1.1 (1–11.8)</td>
<td>2.0 (0–1–9.0)</td>
<td>.1</td>
</tr>
</tbody>
</table>

DISCUSSION

Even though MR imaging has traditionally played a central role in the evaluation and monitoring of patients with DIPG, little is known regarding the biologic and molecular correlates of imaging features such as the presence of enhancement, low diffusivity, and findings on ADC histogram analysis.12,18 Recently, more centers are performing biopsies for DIPG, which has permitted identification of molecular subgroups with distinct clinical characteristics.3,19-21 This work demonstrates the feasibility of a radiogenomic approach to investigate differences among various tumor groups. Specifically, we identified significant differences in volume of enhancing tumor between molecular subgroups and differences in volume of enhancing tumor and ADC histogram parameters across tumors with different histone mutations. We followed a previously validated approach for patients with DIPG, thus, minimizing the risk of introducing methodologic bias in our analysis.12

Molecular characteristics of brain tumors are now widely accepted as important diagnostic criteria for many entities as well as independent prognostic markers.22,23 Castel et al3 investigated the molecular profile of DIPG in 91 children and identified 2 distinct subgroups with mutations in H3.3 (H3F3A) and H3.1 (HIST1H3B/C) histone variants. Tumors with H3F3A mutations had a worse prognosis, with a poor response to radiation therapy and earlier relapse compared with HIST1H3B/C mutated tumors.20 Similar to the observations by Castel et al, we found a strong trend toward shorter OS in patients with H3F3A mutations relative to HIST1H3B/C, though this did not reach statistical significance, likely due to the smaller sample size in our study.

ADC histogram analysis revealed differences across histone mutations, with H3F3A-mutated tumors having lower ADC T2-FLAIR/T2, higher skewness, and higher kurtosis than HIST1H3B/C-mutated tumors. This finding suggests that histogram metrics

after FDR adjustment (P=.04; n = 30) (On-line Table 3). All MGMT+ tumors showed enhancement, most MGMT+/EGFR+ tumors (77%) showed enhancement, and 54% of MGMT-/EGFR- tumors showed enhancement (On-line Table 3). The 3 MGMT+/EGFR- tumors had the highest tumor volume enhancing values, occasionally an order of magnitude higher than those of other molecular groups, including the MGMT+/EGFR+ tumors. No other factor analyzed showed a significant association with molecular groups, including ADC histogram metrics.

Histone Mutation Analysis

Subjects with HIST1H3B/C tumors showed a trend toward improved OS that bordered on significance (P = .0501) compared with subjects with H3F3A tumors (Fig 1). There was no difference in PFS (P = .22) between subjects with H3F3A and HIST1H3B/C tumors.

Tumor volume enhancing (in a subset of patients with enhancing tumor volumes of >0 mL, P = .048), median ADC FLAIR (P = .03), and mode ADC FLAIR (P = .02) were significantly higher in tumors with HIST1H3B/C mutations. Skewness ADC FLAIR (P = .009) and kurtosis ADC FLAIR (P = .03) were significantly higher in tumors with H3F3A mutations. H3F3A mutations had lower ADC values compared with HIST1H3B tumors (Fig 2 and Table 2).

A comparison of ADC T2-FLAIR/T2 mean, median, and mode; skewness; and kurtosis did not show differences between wild-type tumors and grouped histone mutation (H3F3A and HIST1H3B/C) tumors (Table 3). Kaplan-Meier analysis also failed to demonstrate significant differences in OS or PFS between wild-type and grouped histone-mutated tumors (Fig 3).
may help differentiate tumors that have the H3F3A mutation, which carries a worse prognosis, from those with HIST1H3B/C mutations. Poussaint et al.\textsuperscript{12} found that tumors with lower preradiotherapy mean, median, and mode ADC FLAIR (analogous to T2-FLAIR/T2 in our study) had shorter PFS and that tumors with higher skewness and kurtosis had shorter OS and PFS. Although that study did not include pathologic or molecular analysis of the tumors, the findings consistently indicated that ADC histogram metrics can identify tumors with more aggressive biology; it is therefore possible that some of the tumors with these ADC

histogram features in the study by Poussaint et al may have had H3F3A mutations.

The differences in ADC and ADC histogram parameters among histone-mutated tumors is likely multifactorial. As postulated by Poussaint et al.\textsuperscript{12} Lober et al.,\textsuperscript{26} Zukotynski et al.,\textsuperscript{27} Chen et al.,\textsuperscript{11} and Lobel et al\textsuperscript{28} on prior studies of DIPG, and by Nowosielski et al\textsuperscript{29} on studies of adult high-grade gliomas, the lower diffusivity and increased kurtosis possibly reflect higher cellularity, which could be related to the more aggressive biology of H3F3A-mutated tumors. Additionally, Castel et al\textsuperscript{3} reported that the H3.1 tumors had an enrichment in genes associated with glioblastoma with edema, which correlated with exuberant extracellular edema in their histologic analysis; these factors may also contribute to overall higher ADC and lower skewness/kurtosis in H3.1-mutated tumors. A difference between the study by Poussaint et al\textsuperscript{12} and the current study is that we did not find an association of ADC histogram metrics with PFS or OS, which could be related to a larger sample size in the former study, which analyzed approximately 3 times as many patients. However, the significant trends we observed showed an association of other adverse prognostic factors with the more aggressive (H3F3A) tumors.

We did not identify differences in mean, median, mode ADC histogram parameters, or survival between wild-type histone tumors and H3K27M-mutated tumors (collectively), consistent with the results from a study published by Aboian et al.\textsuperscript{30} Similarly, the study by Castel et al\textsuperscript{3} did not identify differences in survival between wild-type tumors and histone-mutated tumors (collectively). Chen et al\textsuperscript{31} found lower ADC in the tumor and peritumoral regions of patients with H3K27M mutations compared with wild-type tumors; however, the patient population analyzed in that study is vastly different, possibly accounting for the discrepancy. For instance, the study by Chen et al included H3K27M tumors outside of the brain stem (spinal cord) and included substantially older subjects (most of subjects were older than 18 years of age).\textsuperscript{31}

In our cohort, higher tumor volume enhancing had a significant association with shorter OS and PFS, as has been shown in
Differences in tumor volume enhancing were also observed between tumors with H3F3A and HIST1H3B/C mutations, a finding that has not been previously reported in the literature.

Most interesting, higher tumor volume enhancing, which is thought to have a negative prognostic association, was higher in HIST1H3B/C tumors, which have a better prognosis compared to tumors with H3F3A mutations.3 We believe that this observation is likely related to the higher expression of genes responsible for angiogenesis in H3.1-mutated tumors, and these findings correlate with preliminary observations described by Castel et al in a subanalysis of their radiologic data. Our sample size was too small to perform a subgroup analysis between enhancing and nonenhancing tumors for each histone mutation; additional work is needed to further elucidate the implications of differences in enhancement in tumors with different histone mutations.24,25 This complex landscape suggests that a multiparametric approach may be useful when evaluating DIPG, because multiple genetic pathways (including MGMT, EGFR, histone) probably account for the pleomorphic MR imaging appearance and clinical course of these tumors, and these factors likely interact with each other to determine the clinical course.31

There are several limitations to this study. First, we conducted our analysis on a small sample size from a single prospective clinical trial. Consequently, our results are preliminary observations that need to be corroborated in a larger separate cohort. Due to the small sample size, we were unable to explore the prognostic implications of differences in enhancement and ADC histogram metrics within individual molecular subgroups and histone variants. Although we identified group differences in diffusion metrics, ADC histogram analysis, and enhancement, the exact biologic substrates for these were not explored. More detailed genetic analyses being performed on this cohort may uncover biologic explanations for these differences. Finally, we analyzed only the baseline MR imaging and did not analyze the changes in any of the baseline parameters with treatment on subsequent MRIs. ADC histogram metrics and tumor enhancing volume could potentially serve as valuable markers of treatment response.

CONCLUSIONS
MR imaging features including enhancement and ADC histogram metrics are correlated with molecular subgroups and histone mutations in children with DIPG. Noninvasive markers that allow identification of molecular subgroups of DIPG could help prognosticate survival and guide therapy. Future studies in a larger cohort are required to verify these findings.

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REFERENCES


