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Chromosome 17p Homodisomy Is Associated With Better Outcome in 1p19q Non-Codeleted and *IDH*-Mutated Gliomas

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Gliomas • Copy number neutral loss of heterozygosity • *TP53* mutation

Abstract

Background. The 1p19q non-codeleted gliomas with *IDH* mutation, defined as "molecular astrocytomas," display frequent *TP53* mutations and have an intermediate prognosis. We investigated the prognostic impact of copy number-neutral loss of heterozygosity (CNLOH) in 17p in this population.

Methods. We analyzed 793 gliomas (206 grade II, 377 grade III, and 210 grade IV) by single nucleotide polymorphism array and for *TP53* mutations.

Results. Homodisomy revealed by CNLOH was observed in 156 cases (19.7%). It was more frequent in astrocytomas and oligoastrocytomas (98/256, 38%) than oligodendrogliomas (28/327, 8.6%; $p < .0001$) or glioblastoma multiforme (30/210, 14.3%; $p < .0001$), tightly associated with *TP53* mutation (69/71 vs. 20/79; $p = 2 \times 10^{-16}$), and mutually exclusive with 1p19q codeletion (1/156 vs. 249/556; $p < .0001$). In the group of *IDH*-mutated 1p19q non-codeleted gliomas, CNLOH 17p was associated with longer survival (86.3 vs. 46.2 months; $p = .004$), particularly in grade III gliomas (overall survival >100 vs. 37.9 months; $p = .007$). These data were confirmed in an independent dataset from the Cancer Genome Atlas.

Conclusion. CNLOH 17p is a prognostic marker and further refines the molecular classification of gliomas. ***The Oncologist*** 2016;21:1131–1135

Implications for Practice: Homodisomy of chromosome 17p (CNLOH 17p) is a frequent feature in *IDH*-mutated 1p19q non-codeleted gliomas (group 2). It is constantly associated with *TP53* mutation. It was found, within this specific molecular group of gliomas (corresponding to molecular astrocytomas), that CNLOH 17p is associated with a much better outcome and may therefore represent an additional prognostic marker to refine the prognostic classification of gliomas.

Introduction

Independently of histological grading, gliomas can be separated into three distinct prognostic subgroups according to the presence of *IDH* mutation and 1p19q codeletion: group 1, glioma with 1p19q codeletion, has the best survival; group 2, non-codeleted glioma with *IDH* mutation, has an intermediate prognosis; and group 3, *IDH* wild-type glioma, has the poorest outcome [1–3]. Groups 1 and 2 also differ by the occurrence of mutually exclusive mutations: *TERT* promoter (90%), *CIC* (50%–60%), and *FUBP1* (15%–20%) for group 1 and *ATRX* mutation (associated with the alternative lengthening telomeres phenotype) and *TP53* mutation for group 2 [2–4]. Recent single nucleotide polymorphism (SNP) analysis showed several cases of copy neutral loss of heterozygosity (CNLOH) with duplication of the retained allele. The presence of CNLOH in glial tumors has been reported to affect several genomic regions [5–9]. In a recent report on anaplastic oligodendrogliomas, CNLOH frequently affected the short arm of chromosome 17 [5]. Moreover, Yin et al. described eight cases with CNLOH 17p in a series of 55 glioblastomas [9]. To date, the frequency and prognostic significance of this alteration have not been investigated.

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In this study, we investigated the presence of CNLOH 17p in a large cohort of grade II–IV glial tumors, analyzed the associations with *TP53* mutation and other molecular alterations, and investigated the prognostic impact of CNLOH 17p.

Patients and Methods

Patients and Tissue Samples

Patients were selected according to the following criteria: histologic diagnosis of primary glial tumor, clinical data and follow-up available in the neuro-oncology database (OncoNeurotek, Groupe Hospitalier Pitié Salpêtrière, Paris, France), and written informed consent. Corresponding clinical annotations were collected from the neuro-oncology department database. As a duplication cohort, we used the DNA sequencing, copy number variant (level 1 copy number data), and survival data (level 3) from lower-grade gliomas (LGGs) of the Cancer Genome Atlas (TCGA) (http://cancergenome.nih.gov).

DNA Isolation and SNP Array

Tumor DNA from cryopreserved samples was extracted using the QIAmp DNA Midi Kit (Qiagen, Hilden, Germany, http://www.qiagen.com) according to the manufacturer's instructions. DNA was extracted from blood samples by conventional saline method, quantified using a NanoVue spectrophotometer, and qualified by agarose gel electrophoresis. Tumor DNA was run on an Infinium Illumina Human 610-Quad SNP array (Illumina, San Diego, CA, http://www.illumina.com). Array processing, using 250 ng tumor DNA, was outsourced to Integragen, Évry, France. Extracted data using Feature Extraction software were imported and analyzed using Nexus 5.1 (Biodiscovery, El Segundo, CA, http://www/biodiscovery.com), as previously described [10]. The confirmatory cohort from LGG TCGA was analyzed using PennCNV-Affy from the PennCNV algorithm [11] to convert raw CEL files from LGG TCGA into log R ratio and B-allele frequency. Log R ratio and B-allele frequency files were used to perform allele-specific copy number analysis with GC correction using ASCAT (version 2.4) [12]. We considered loss of heterozygosity in a given chromosome region when $\geq$95% of SNP probes in a DNA segment of at least 500 kb exhibited B-allele frequencies $\geq$0.8 and $\leq$0.2. Loss of heterozygosity with a copy number of 2 was considered CNLOH. Only terminal CNLOH on chromosome 17p with a minimum size of 5 Mb was considered. Molecular characterization of glioma samples (*IDH1/2* mutation, *TERT* promoter mutation, and *MGMT* promoter methylation) was performed as previously described [13].

TP53 Pyrosequencing

Coding exons (2–11) of *TP53* gene were first amplified using primers detailed in supplemental online Table 1. Amplification conditions were 94°C for 3 minutes followed by 45 cycles of 94°C for 15 seconds, 60°C for 45 seconds, and 72°C for 1 minute, with a final step at 72°C for 8 minutes. Polymerase chain reaction (PCR) products were purified conforming to the Agencourt AMPure XP PCR purification protocol (Beckman-Coulter, Nyon, Switzerland, http://www.beckmancoulter.com) with the Biomek 3000 Automation Workstation. Universal tailed amplicon resequencing approach (454 Sequencing Technology; Roche, Basel, Switzerland, http://www.roche.com) was used for sequencing of coding exons of *TP53*. This system includes a second PCR, aiming for multiplex identifiers and incorporation of 454 adaptors, an emulsion PCR according to the emPCR Amplification Method Manual Lib-A protocol (GS Junior Titanium Series, Roche), enrichment, and pyrosequencing according to the Sequencing Method Manual (Roche). Sequence analysis was performed using CLC Genomics Workbench software.

Table 1. Frequency of CNLOH 17p according to glioma histologic subtype

		CNLOH 17p	
Subtype and histology	***n***	***n***	**%**
Astrocytoma/oligoastrocytoma	256	98	38
Grade II	104	42	40
Grade III	152	56	37
Oligodendroglioma	327	28	8.6
Grade II	102	8	7.8
Grade III	225	20	8.9
Glioblastoma	210	30	14.3

Abbreviations: CNLOH, copy number-neutral loss of heterozygosity.

TP53 Sanger Sequencing

TP53 mutations identified by pyrosequencing were confirmed by direct Sanger sequencing. Tumor DNA was first amplified and purified using the same primers and conditions described for pyrosequencing. Sequencing reactions were performed in both orientations using Big-Dye Terminator Cycle Sequencing Ready Reaction (PerkinElmer, Waltham, MA, http://www.perkinelmer.com). Extension products were purified with the Agencourt CleanSEQ protocol according to the manufacturer's instructions (Beckman-Coulter). Purified sequences were analyzed on an ABI Prism 3730 DNA Analyzer (Applied Biosystems, Foster City, CA, http://www.appliedbiosystems.com). Forward and reverse sequences were systematically analyzed using Chromas Lite software.

Statistical Analysis

We used chi-square and Fisher exact test to compare genotype distribution. The association with continuous variables was calculated with the Mann-Whitney test. Overall survival (OS) was defined as the time between diagnosis and death or last follow-up. Patients who were alive at last follow-up were considered as a censored event in analysis. Progression-free survival (PFS) was defined as the time between diagnosis and recurrence or last follow-up. Patients who were recurrence-free at last follow-up were considered as a censored event in analysis. To find clinical or genomic factors related to OS or PFS, survival curves were calculated according to the Kaplan-Meier method, and differences between curves were assessed using the log-rank test. Variables with a significant p value were used to build a multivariate Cox model. Two-sided p values $< .05$ were considered significant.

Table 2. Association of CNLOH 17p with common molecular alterations in gliomas

	Present		Absent		
CNLOH 17p	**Frequency**	**%**	**Frequency**	**%**	***p* value**
EGFR amplification	6/156	3.8	99/637	15.6	<.0001
CDKN2A deletion	23/156	14.7	165/637	25.9	.0032
IDH mutation	114/141	80.9	309/556	55.6	<.0001
1p19q codeletion	1/156	0.6	249/637	39.1	<.0001
MDM2 amplification	0/154	0.0	14/637	2.2	.0173
CDK4 amplification	8/155	5.2	20/637	3.1	NS
TERT promoter mutation	18/74	24.3	159/248	64.1	<.0001
MGMT promoter methylation	17/23	73.9	78/140	55.7	NS
Chr10q loss	29/156	18.6	212/637	57.8	.0003
TP53 mutation	69/71	97.2	20/79	25.3	<.0001

Abbreviations: Chr, chromosome; CNLOH, copy number-neutral loss of heterozygosity; NS, not significant.

Results

We screened the genomic profiles of 793 gliomas (206 grade II, 377 grade III, and 210 grade IV) for the presence of CNLOH 17p. In the whole cohort, we identified 156 cases with CNLOH 17p (19.7%), affecting the whole chromosome 17 in 14 cases (9.0%), the whole short arm of chromosome 17 in 15 cases (9.6%), and only the telomeric portion of 17p in 127 cases (81.4%), including in all cases the *TP53* locus. The mean size of the affected region was 21.6 ± 1.1 Mb (range 7.7–80.9 Mb) (supplemental online Fig. 1A, 1B). We also screened a series of 96 constitutional DNA samples. We did not find any CNLOH 17p in blood DNA, confirming this as a somatic event.

CNLOH 17p affected 50 of 206 grade II (24.3%), 76 of 377 grade III (20.2%), and 30 of 210 grade IV gliomas (14.3%). CNLOH 17p was more frequent in astrocytomas and oligoastrocytomas (98/256, 38%) than oligodendrogliomas (28/327, 8.6%; $p < .0001$) or glioblastoma multiforme (30/210, 14.3%; $p < .0001$) (Table 1).

We investigated the presence of *TP53* mutation by pyrosequencing. Each nonsilent variation was then validated by Sanger sequencing. Of the 71 tumors with CNLOH 17p and available DNA, 97.2% (69/71) were mutated on the *TP53* gene. Electropherograms showed a pattern of homozygous mutation (supplemental online Fig. 2A) in all cases. Missense mutations were the most frequent (58/71, 81.7%), compared with nonsense mutations (8/71, 11.3%) and frameshifts (5/71, 7.0%). Strikingly, one of the two nonmutated tumors had a focal homozygous deletion of *TP53* locus (supplemental online Fig. 3). In all, the *TP53* gene was altered in all but one tumor with CNLOH 17p (70/71, 98.6%). Interestingly, P53 was overexpressed by immunohistochemistry in the remaining nonaltered case, suggesting abnormal P53 sequestration (data not shown).

In non-CNLOH 17p gliomas, *TP53* mutational status was available in 79 tumors. We identified 24 *TP53* mutations (25.3%; $p < .0001$) on 20 tumors, with four tumors having a double variant consisting of 21 (80.8%) missense mutations, four (15.5%) nonsense mutations, and one (3.8%) frameshift. In all these non-CNLOH 17p gliomas, electropherograms showed a heterozygous pattern of *TP53* mutation (supplemental online Fig. 2B). Based on the *TP53* database reported by Edlund et al. [14], we found that 86 of 97 (89%) of these mutations affected the *TP53* DNA binding domain (65/71 in the CNLOH 17p group and 21/26 in the control group; not significant). All mutations are predicted to be transcriptionally inactive.

Table 3. Relative frequency of CNLOH 17p in molecular groups 1, 2, and 3 of grade II–III gliomas

	Present		
CNLOH 17p	**Frequency**	**%**	***p* value**
Group 1 (1p19q codeletion)	1/225	0.44	<.0001
Group 2 (*IDH* mutation without 1p19q codeletion)	85/152	55.92	—
Group 3 (*IDH* wild-type)	7/98	7.14	<.0001

p value determined by Fisher's exact test with group 2.
Abbreviations: —, no data; CNLOH, copy number-neutral loss of heterozygosity.

We next investigated the association of CNLOH 17p with other molecular alterations commonly found in gliomas (Table 2). CNLOH 17p was mutually exclusive with 1p19q codeletion (1/156 vs. 249/556; $p < .0001$) and was associated with *IDH* mutation (114/141 vs. 309/556; $p < .0001$). In grade II and III gliomas, CNLOH 17p was associated with the 1p19q non-codeleted *IDH*-mutated gliomas (group 2) (55.9% of group 2 tumors compared with groups 1 and 3) (Table 3).

We then evaluated the prognostic impact of CNLOH 17p. We did not find any impact on PFS or OS for grade II–IV gliomas with available clinical data (supplemental online Fig. 4). This is not surprising, because CHLOH 17p is strongly associated with the *TP53* mutation, which itself is associated with group 2 gliomas, which have an intermediate prognosis (Fig. 1A). We therefore considered specifically the prognostic impact of CNLOH 17p in group 2 and found an association with a much better outcome (OS 86.3 vs. 46.2 months; $p = .004$) (Fig. 1B). The difference was particularly clear in grade III gliomas (OS >100 vs. 37.9 months; $p = .007$) (Fig. 2) but was not found in grade II and IV gliomas.

We then entered into the Cox model the major histological and biological prognostic markers, i.e., the grading and the molecular subgroup (1p19q codeletion, *IDH* mutation, *IDH*

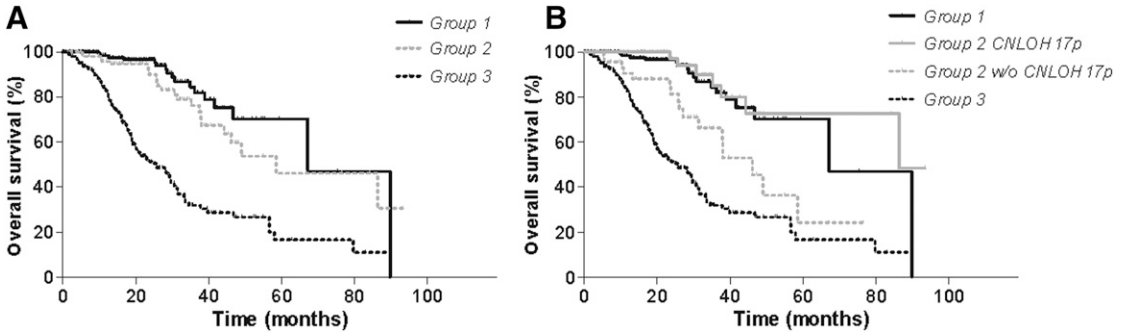

Figure 1. **(A)** Prognostic classification of grade II–IV gliomas according to 1p19q and *IDH* status (groups 1, 2, and 3). **(B)** Prognostic impact of CNLOH 17p in group 2. Survival times were compared using log-rank test (Mantel-Cox). The presence of CNLOH 17 p in group 2 was associated with better outcome (OS 86.3 vs. 46.2 months for group 2 with and without CNLOH 17p, respectively; $p = .004$).

Abbreviations: CNLOH, copy number-neutral loss of heterozygosity; OS, overall survival; w/o, without.

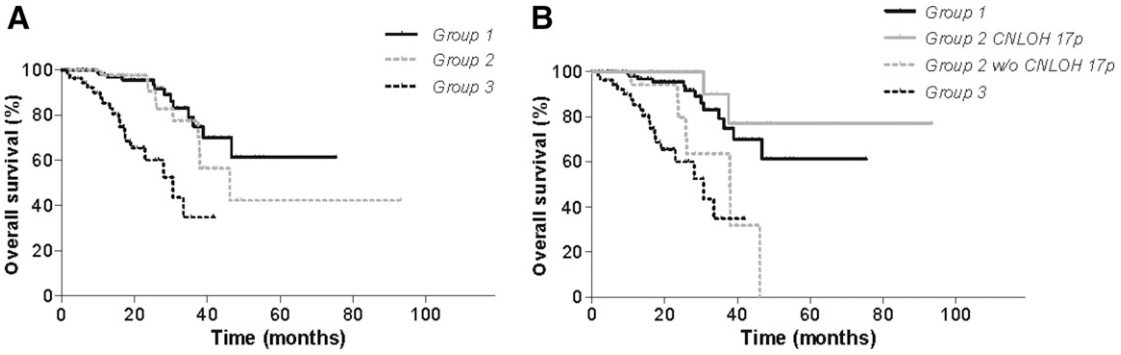

Figure 2. **(A)** Prognostic classification of grade III gliomas according to 1p19q and *IDH* status (groups 1, 2, and 3). **(B)** Prognostic impact of CNLOH 17p in group 2. Survival times were compared using log-rank test (Mantel-Cox). The presence of CNLOH 17p in group 2 was associated with better outcome (OS >100 vs. 37.9 months for group 2 with and without CNLOH 17p, respectively; $p = .007$).

Abbreviations: CNLOH, copy number-neutral loss of heterozygosity; OS, overall survival; w/o, without.

wild-type): both were strongly predictive of outcome (hazard ratios 2.094 and 1.840, $p = 7 \times 10^{-7}$ and 2×10^{-5}, respectively), but the negative prognostic impact of CNLOH 17p remained significant (hazard ratio 1.641; $p = .04$). Because CNLOH 17p is specifically found in group 2 (IDH-mutated non-codeletion gliomas), we performed multivariate analysis specifically in this group, entering CNLOH 17p, grade, *EGFR* amplification, *CDKN2A* deletion, and *TP53* mutation. We found that CNLOH 17p was the strongest (odds ratio [OR] for non-CNLOH p17 = 3.58) and the most significant ($p = .014$) prognostic marker.

To confirm this result, we analyzed survival data from 142 LGGs from TCGA with *IDH1*/*IDH2* mutations and no 1p19q codeletion. Despite the high rate of censured data, we found that CNLOH 17p, including the *TP53* locus, was associated with better outcome (OR = 0.27; $p = .026$) (supplemental online Fig. 5) [11].

Discussion

Using SNP array, we found that CNLOH 17p is a frequent alteration in gliomas. A similar mechanism has also been reported in other malignancies [15]. Strikingly, CNLOH affects selectively 17p and not (or only marginally) the other chromosome segments, as shown by a recent whole-exome sequencing analysis [2, 16]. We found CNLOH 17p to be almost systematically associated with *TP53* mutation or deletion (70 of 71 samples). The sequence analysis showed a homozygous mutation in all cases, suggesting that during the mechanism of tumorigenesis, the normal arm of chromosome 17p is lost and the altered chromosome arm is duplicated, leading to a homozygous mutation of *TP53* [9, 17–19].

In our series, CNLOH 17p is mutually exclusive with 1p19q codeletion and is associated with *IDH* mutation. Regarding the three molecular subgroups [1–3], CNLOH 17p samples were mostly found in group 2, the 1p19q non-codeleted *IDH*-mutated group, which is associated with *TP53* mutation (85/152 vs. 1/225 in the 1p19q codeleted group and 7/98 in the non-1p19q codeleted, non-*IDH* mutated group).

We therefore analyzed the prognostic impact of CNLOH 17p in this particular subgroup (*IDH* mutated, non-1p19q codeleted). We found that tumors harboring CNLOH 17p had a better OS than tumors without CNLOH 17p and similar to that of 1p19q codeleted tumors (Fig. 2B). The upcoming World Health Organization classification of gliomas will integrate molecular markers; in this setting, the replication of this finding in the independent TCGA series allows generalization of our conclusion; thus we propose CNLOH 17p as a stratification marker in this subgroup defined as molecular astrocytomas [20].

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Disclosures

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