



HAL
open science

High mitochondrial DNA copy number is associated with longer survival in young patients with glioblastoma

Laure-Marie Dardaud, Céline Bris, Valérie Desquiret-Dumas, Blandine Boisselier, Emeline Tabouret, Karima Mokhtari, Dominique Figarella-Branger, Audrey Rousseau, Vincent Procaccio

► To cite this version:

Laure-Marie Dardaud, Céline Bris, Valérie Desquiret-Dumas, Blandine Boisselier, Emeline Tabouret, et al.. High mitochondrial DNA copy number is associated with longer survival in young patients with glioblastoma. *Neuro-Oncology*, 2019, 21 (8), pp.1084-1085. 10.1093/neuonc/noz072 . hal-02616951

HAL Id: hal-02616951

<https://univ-angers.hal.science/hal-02616951v1>

Submitted on 3 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Letter to the Editor

High mitochondrial DNA copy number is associated with longer survival in young patients with glioblastoma

Glioblastoma (GB) is the most common and most aggressive form of diffuse glioma, with a median overall survival of 15 months after standard of care.¹ Young GB patients (<40 years old) may carry isocitrate dehydrogenase 1 or 2 (*IDH1/2*) mutations or, in rare instances, harbor *H3F3A* or *HIST1H3B* mutations. Other cases are wild-type for those genes and harbor gain of chromosome (chr) 7, loss of chr 10, and epidermal growth factor receptor (*EGFR*) amplification (amp). *IDH1/2* mutations are associated with longer survival (24 mo), whereas histone *H3F3A/HIST1H3B* gene mutations are associated with shorter survival (9–12 mo).¹ Novel reliable prognostic factors are needed for *IDH* and *H3* wild-type GB.

Mitochondria are responsible for the production of ATP through oxidative phosphorylation (oxphos). The 16569 nucleotide long mitochondrial DNA (mtDNA), present in hundreds to thousands of copies per cell, is circular, intron-less and exclusively maternally inherited. It encodes, among others, 13 essential polypeptides required for oxphos.² High mtDNA copy number has been associated with variable clinical outcomes in different cancer types.³

The mtDNA copy number was assessed by real-time quantitative PCR as described elsewhere⁴ in 67 primary GB developed in patients aged between 18 and 40 years. Clinical, molecular, and survival data were available for all patients. In addition, whole mitochondrial genome next-generation sequencing (NGS) was performed in 18/67 GB. Written informed consent was obtained from all individual participants with approval of the research ethics committee of Angers University Hospital.

In the overall cohort, the sex ratio (M/F) was 1.3; the median age at diagnosis was 35 years, and the median overall survival was 14.3 months. Seventeen of 67 (25.3%) cases harbored *IDH1-R132H* mutation; 30/67 (44.8%) had chr 7 gain and chr 10 loss and/or *EGFR* amp (identified by single nucleotide polymorphism arrays); and 4/67 (6%) harbored *H3F3A* or *HIST1H3B* mutations. The remaining 16 cases (23.9%) had none of the above-mentioned genetic alterations.

The mtDNA/nuclear DNA ratio ranged from 25.6 to 3882.4 and was subdivided into 2 groups: low and high according to the median of the mtDNA copy number (median 194.9). Thirty-four patients (50.7%) displayed a low ratio (ratio \leq median), whereas 33 (49.3%) displayed a high ratio ($>$ median). A log-rank test was performed: the overall survival in the high vs low

group was significantly longer: 31.8 months vs 12.9 months ($P = 0.013$; hazard ratio = 2.338; 95% CI [1.196; 4.571]) (Fig. 1A). Overall survival was also significantly longer for the high versus low GB patients within the genetic subgroup chr7+/chr10-/*EGFR* amp (37.8 mo vs 12.1 mo; $P = 0.0115$) (Fig. 1B). There was still a trend toward longer survival in the high vs low groups within the other genetic subgroups (*IDH*-mutant and no genetic alteration) except for the *H3*-mutant GB (only 4 patients in this subgroup) (Fig. 1B). Of note, *IDH* status and mtDNA copy number were 2 independent variables ($P = 0.36$, Pearson's chi-square test). In addition, NGS analysis did not reveal the accumulation of somatic mtDNA variants in 18/67 GB (data not shown), as opposed to what has been previously reported in GB.³

The present study revealed that higher mtDNA copy number was significantly correlated with better overall survival in young adult GB. Of great interest, high mtDNA level is linked to oxidative metabolism, which is known to decrease tumor aggressiveness, and to cell differentiation.⁵ The modulation of mtDNA copy number in a model of GB was recently shown to induce changes to DNA methylation and gene expression of the nuclear genome, and thus to modulate the tumorigenic potential of GB cells in vivo.⁶ Therapeutics to increase mtDNA copy number might induce tumor cell differentiation and slow disease progression. Further analyses on larger cohorts of GB patients of all ages are needed, especially in the older population who is the most affected by the disease. In conclusion, our study indicates that mtDNA copy number may be a novel prognostic biomarker in GB patients.

Keywords

glioblastoma | mitochondrial genome | mtDNA copy number | prognosis and survival | young adults

Funding

None.

Acknowledgments

We thank the Public Assistance–Hospital of Marseille (AP-HM) Tumor Bank (authorization number: AC-2018–31053; CRB BB-0033-00097) and the French Glioblastoma Biobank for providing samples.

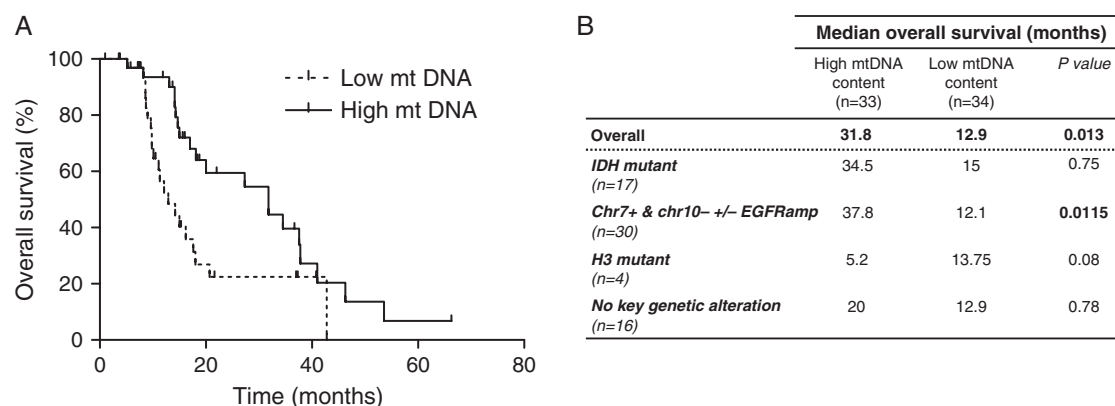


Fig. 1 Overall survival of young GB patients according to the mtDNA copy number level (high vs low). (A) Kaplan–Meier survival curves in young adult GB stratified according to the tumor mtDNA content. (B) Median overall survival according to the tumor mtDNA content (high vs low) in the whole cohort and according to the genetic subgroups. In the high group, there were 10 IDH-mutant GB (30.3%), one H3-mutant GB (3%), 12 GB with chr7+/chr10–/EGFR amp (36.4%) and 10 cases without key genetic alteration (30.3%). The low group comprised 7 IDH-mutant GB (20.6%), 3 H3-mutant GB (8.8%), 18 GB with chr7+/chr10–/EGFR amp (53%), and 6 cases with no key genetic alteration (17.6%). Of note, the genetic subgroups were equally distributed between both groups (high vs low). Within the IDH-mutant subgroup, there was a trend toward longer survival in the high vs low GB but the difference did not reach statistical significance.

Conflict of interest statement. None declared.

Laure-Marie Dardaud, Céline Bris, Valérie Desquret-Dumas, Blandine Boisselier, Emeline Tabouret, Karima Mokhtari, Dominique Figarella-Branger, Audrey Rousseau,[†] and Vincent Procaccio[†]

Department of Cellular and Tissue Pathology, University Hospital of Angers, Angers, France (L.M.D., B.B., A.R.); Department of Genetic Biochemistry, University Hospital of Angers and MitoLab, MitoVasc Institute, National Institute of Health and Medical Research (INSERM), University of Angers, Angers, France (C.B., V.D.M., V.P.); Center for Research in Cancerology and Immunology Nantes/Angers, INSERM, University of Nantes, University of Angers, Angers, France (B.B., A.R.); University of Aix-Marseille, Institute of Neurophysiopathology, Hospital Timone, Marseille, France (E.T., D.F.B.); Neuro-Oncology Unit, Hospital Timone, Marseille, France (E.T.); Raymond Escourolle Neuropathology Department and OncoNeuroThèque, University Hospitals La Pitié Salpêtrière–Charles Foix, Paris, France (K.M.); Department of Pathological Anatomy and Neuropathology, Hospital Timone, Marseille, France (D.F.B.)

[†]Contributed equally to this work.

Corresponding Authors: Vincent Procaccio, MD, PhD, Biochemistry and Genetic Laboratory, Angers University Hospital, 4 rue Larrey, 49933 Angers, France (ViProcaccio@chu-angers.fr); Audrey Rousseau, MD, PhD, Pathology Department, Angers University Hospital, 4 rue Larrey, 49933 Angers, France (auroousseau@chu-angers.fr).

References

- Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. *WHO Classification of Tumours of the Central Nervous System*. IARC Lyon 2016.
- Wallace DC, Fan W, Procaccio V. Mitochondrial energetics and therapeutics. *Annu Rev Pathol*. 2010;5:297–348.
- Larman TC, DePalma SR, Hadjipanayis AG, et al; Cancer Genome Atlas Research Network. Spectrum of somatic mitochondrial mutations in five cancers. *Proc Natl Acad Sci U S A*. 2012;109(35):14087–14091.
- Boucret L, Bris C, Seegers V, et al. Deep sequencing shows that oocytes are not prone to accumulate mtDNA heteroplasmic mutations during ovarian ageing. *Hum Reprod*. 2017;32(10):2101–2109.
- Liberti MV, Locasale JW. The Warburg effect: how does it benefit cancer cells? *Trends Biochem Sci*. 2016;41(3):211–218.
- Sun X, St John JC. Modulation of mitochondrial DNA copy number in a model of glioblastoma induces changes to DNA methylation and gene expression of the nuclear genome in tumours. *Epigenetics Chromatin*. 2018;11(1):53.