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DIPG-43. CLINICAL AND MOLECULAR CHARACTERISTIC OF
A NEW SUBTYPE OF DMG, H3K27-ALTERED WITH MAPK-
ACTIVATING CO-DRIVER MUTATIONS.
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Medhi Touat⁸, Marc Sanson⁸, Kevin Beccaria⁹, Thomas Blauwblomme⁹, Volodia Dangouloff-Ros¹⁰, Nathalie Boddaert¹⁰, Pacale Varlet^{3,4}, Marie-Anne Debily^{1,11}, Jacques Grill^{1,2}, David Castel^{1,2}, ¹U981, Molecular Predictors and New Targets in Oncology, Team Genomics and Oncogenesis of Pediatric Brain Tumors, Inserm, Gustave Roussy, Université Paris-Saclay, Villejuif, France. ²Département de Cancérologie de l'Enfant et de l'Adolescent, Gustave Roussy, Université Paris-Saclay, Villejuif, France. ³Department of Neuropathology, GHU Paris-Psychiatrie et Neurosciences, Sainte-Anne Hospital, Paris, France. ⁴Inserm, UMR 1266, IMA-Brain, Institut de Psychiatrie et Neurosciences de Paris, Paris, France. ⁵Department of Oncology, Pontchaillou Hospital, Rennes, France. ⁶Department of Neurosurgery, Rennes University Hospital, Rennes, France. ⁷Neurooncology Unit, IRCCS C. Mondino Foundation, Pavia, Italy. ⁸Sorbonne Université, Inserm U1127, CNRS UMR 7225, Institut du Cerveau, ICM, AP- HP, Hôpitaux Universitaires La Pitié Salpêtrière - Charles Foix, Service de Neurologie 2-Mazarin, F-75013, Paris, France, Paris, France. ⁹Department of Pediatric Neurosurgery, Necker Enfants Malades Hospital, APHP, Université Paris Cité, Paris, France. ¹⁰Department of Neuroradiology, Hôpital Necker-Enfants Malades, APHP, Paris, France. Université Paris Cité, Paris, France. ¹¹Département de Biologie, Université Evry Paris-Saclay, Evry, France

Diffuse midline gliomas (DMG) represent a big challenge in neuro-oncology. These tumors occur more frequently in children and are presently incurable. They are characterized by a K27M substitution in H3.1 or H3.3 histone tail or the overexpression of *EZH1* (EZH Inhibitory Protein). These three alterations induce a global loss of trimethylation in H3K27 with a specific epigenic and transcriptomic remodeling. The additional oncogenic events and the clinical behavior are also distinct according to the driver event. Based on these differences, the H3K27-altered DMG is now classified in 4 subtypes by the latest edition of the WHO Classification of CNS tumors. Even with this new subclassification, the H3.3K27M subgroup still appears heterogeneous. Recent publications reported that rare patients presenting a co-occurrence of H3.3K27M with *BRAF* or *FGFR1* alterations tend to have a better prognosis.

To better study the role of these co-driver alterations that activate the mitogen activated protein kinase (MAPK) signaling, we assembled a large pediatric and adult cohort of H3K27-altered DMG comprising 25 new DMG patients mutated in *FGFR1* or *BRAF*^{V600E} and 37 previous cases from the literature. We performed a comprehensive histological, radiological, genomic, transcriptomic and DNA methylome analysis on this extended cohort. Interestingly, the results show clear differences with other DMG subtypes, including: specific DNA methylation profile, senescence signature, better overall survival (median around 3 years), older age at diagnosis, specific histological and radiological presentations with calcifications or more circumscribed tumors. Additionally, in specific cases, we show that the MAPK-activating mutation occurred subsequently to the histone H3K27M mutation.

In conclusion, DMG, H3K27-altered harboring MAPK activating mutations represent a new subtype of DMG also frequent in adults, and deserve further attention with respect to specific therapeutic challenges.