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Letter to the Editor

IDH2 mutations are commonly associated with 1p/19q codeletion in diffuse adult gliomas

Diffuse gliomas are classified according to the 2016 World Health Organization (WHO) Classification of Tumors of the Central Nervous System,[1] which combines histological and molecular features. Diagnosis requires the assessment of mutations in the isocitrate dehydrogenase genes (*IDH1* and *IDH2*), key genetic alterations characterizing gliomas with favorable outcome.[2]

Because IDH1 and IDH2 are highly similar enzymes, the WHO classification, as most of the current studies, combines these mutations into the same molecular group; however, it is unclear whether these tumors share the same characteristics.

We analyzed data from 1517 patients included in the French POLA Network to investigate differences between *IDH1*- and *IDH2*-mutant gliomas.

Inclusion criteria were the written consent of the patient for clinical data collection and genetic analysis and sufficient material for molecular studies allowing classification according to the 2016 WHO classification.

IDH1-R132H mutational status was evaluated using automated immunohistochemistry in all cases (n = 1517). Direct sequencing[3] was performed in 978 cases and demonstrated *IDH* mutation in 573 cases (this includes confirmation of *IDH1-R132H* mutation in 468 cases, other *IDH1* mutations in 61 cases, and *IDH2* mutation in 44 cases). The 1p/19q codeletion status was determined based on single nucleotide polymorphism arrays, comparative genomic hybridization arrays, and/or microsatellite marker analysis.[3] The following data were recorded: age, sex, follow-up, and MRI features (tumor location, extension, contrast enhancement, edema). All statistical analysis was done using IBM SPSS statistics software version 23. Chi-square test was used to compare qualitative variables. Continuous variables were compared using the Mann–Whitney U-test, and the Kaplan–Meier method was used to estimate survival distributions.

Among the 1517 patients, 1025 had an *IDH*-mutant tumor: 96% were *IDH1*-mutant and 4% *IDH2*-mutant. Integrated diagnoses are summarized in Fig. 1. The frequency of 1p/19q codeletion was higher in the *IDH2*-mutant group compared with the *IDH1*-mutant group (91% vs 48%, $P < 0.001$).

Wang and coworkers previously reported higher frequency of 1p/19q codeletion in *IDH2*-mutant gliomas (9/18 samples) compared with *IDH1*-mutant.[4] The percentage of each category in our study does not reflect the normal distribution of glioma because of the inclusion criteria in the POLA Network (ie, high-grade glioma with oligodendroglial component). However, the higher proportion of 1p/19q codeleted glioma in the *IDH2*-mutant group cannot be attributed to the inclusion criteria.

Because the main population of glioma associated with *IDH2* mutation was 1p/19q codeleted anaplastic oligodendroglioma, we focused on this subgroup to search for differences compared with *IDH1* mutation. Among these patients (n = 474), we did not observe any difference in terms of age, sex, progression-free survival, or overall survival between *IDH1*- and *IDH2*-mutant tumors. However, *IDH2*-mutant anaplastic oligodendrogliomas presented more frequently with multilobar extension (56% of the *IDH2*-mutant vs 35% of the *IDH1*-mutant, P = 0.015) and edema (79% vs 57%, P = 0.02). Furthermore, bifrontal location with corpus callosum involvement was more frequent in *IDH2*-mutant compared with *IDH1*-mutant tumors (41% vs 16%, $P < 0.001$).

IDH mutation is supposed to be one of the first "hits" of gliomagenesis,[5] resulting in production of an oncometabolite, D-2-hydroxyglutarate (D-2HG), which impacts the α-ketoglutarate–dependent dioxygenase functions. Previous studies demonstrated that the potential for IDH-mutant enzymes to produce D-2HG depends on the mutation type.[6] Based on our observations, we could hypothesize that the higher D-2HG accumulation induced by *IDH2* mutation may lead to a phenotype that is favorable to 1p/19q chromosomal loss. It may also impact distinct cellular pathways that promote a more invasive phenotype. Whether *IDH1* or *IDH2* mutations impact distinct glial precursor cells with differential invasive properties remains to be elucidated.

In conclusion, our results illustrate that *IDH2*-mutant gliomas are commonly associated with 1p/19q codeletion. Most of *IDH2*-mutant anaplastic oligodendroglioma 1p/19q codeleted are multilobar. Understanding the genomic events involved in these specificities may represent a step forward for therapeutic development.

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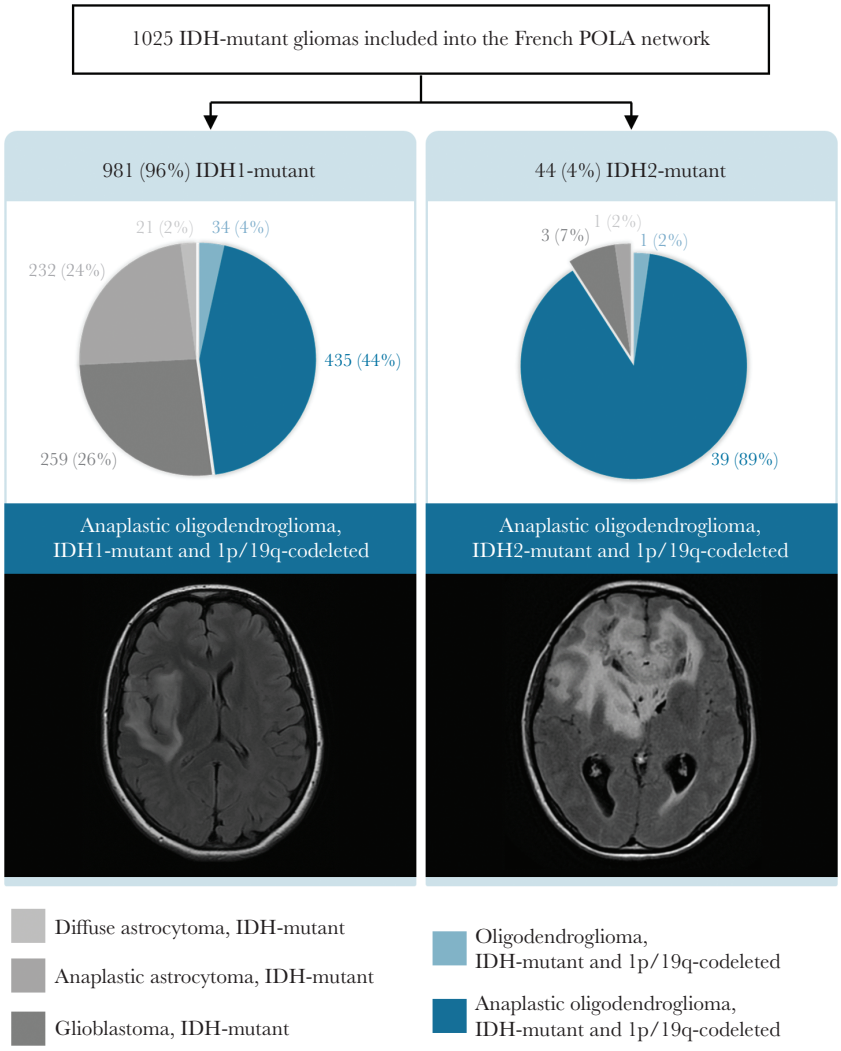

Fig. 1 Integrated diagnosis of the 1025 *IDH*-mutant cases of the French POLA cohort according to the updated fourth WHO classification and representative fluid attenuated inversion recovery MRI axial sections among the subgroups of anaplastic oligodendroglioma, *IDH*-mutant, and 1p/19q codeleted.

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References

1. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol*. 2016;131(6):803–820.
2. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. *N Engl J Med*. 2009;360(8):765–773.
3. Tabouret E, Nguyen AT, Dehais C, et al.; For POLA Network. Prognostic impact of the 2016 WHO classification of diffuse gliomas in the French POLA cohort. *Acta Neuropathol*. 2016;132(4):625–634.
4. Wang HY, Tang K, Liang TY, et al. The comparison of clinical and biological characteristics between IDH1 and IDH2 mutations in gliomas. *J Exp Clin Cancer Res*. 2016;35:86.
5. Watanabe T, Nobusawa S, Kleihues P, Ohgaki H. IDH1 mutations are early events in the development of astrocytomas and oligodendrogliomas. *Am J Pathol*. 2009;174(4):1149–1153.
6. Ward PS, Lu C, Cross JR, et al. The potential for isocitrate dehydrogenase mutations to produce 2-hydroxyglutarate depends on allele specificity and subcellular compartmentalization. *J Biol Chem*. 2013;288(6):3804–3815.