Letter: Is Developmental Venous Anomaly an Imaging Biomarker of *PIK3CA* Mutated Gliomas?

To the Editor:

Phosphoinositide 3-kinase catalytic subunit alpha (*PIK3CA*) gene encodes the p110α catalytic subunit of phosphoinositide 3-kinase (PI3K), which phosphorylates phosphatidylinositol to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). *PIK3CA*, a component of the PI3K/protein kinase B (*AKT*)/mammalian target of rapamycin (*mTOR*) signalling pathway, is considered as a major oncogene in human cancers. Missense mutations include especially the E542K and E545K substitutions in the helical domain and the H1047R change in the kinase domain. Cell-based analyses confirmed that these hotspot mutations confer transformation via constitutive activation of p110α. In cerebral gliomas, *PIK3CA* mutations have been observed in 17% to 27% of adult cases and in 21% of pediatric cases.[1,2] *PIK3CA* postzygotic mutations have also been reported in congenital mosaic overgrowth syndromes: 1) congenital lipomatous overgrowth with vascular, epidermal, and skeletal anomalies (CLOVES) syndrome; 2) megalencephaly syndromes; 3) Cowden-like syndromes; and 4) macrodactyly. In addition, somatic mutations of the *PIK3CA* gene in lymphatic or vascular endothelial cells are associated with the development of lymphatic[3] and venous malformations.[4] The latter may explain the clinical observation of the association between the presence of facial venous malformations and cerebral developmental venous anomalies (DVAs).[5]

We have recently observed an increased prevalence of DVAs in adult patients with diffuse gliomas (21.5%-23.5%)[6] and in pediatric patients with diffuse intrinsic pontine gliomas (24.1%), in contrast to other cerebral neoplasms.[7] This association suggests a possible common underlying role of *PIK3CA* and related mutations in the development of DVAs and gliomas. Interestingly, the observed increase in DVA frequency is 2-fold in association with gliomas and facial venous malformations. This can be of great clinical and practical relevance since the identification of a brain DVA in the MRI workup of a glioma patient may serve as an imaging biomarker of a mutation in the *PIK3CA* gene.

To this end, we propose to perform accurate RNA-sequencing and/or DNA-sequencing (targeted panels or whole exome sequencing) on formalin-fixed and paraffin-embedded or frozen cerebral DVA-associated glioma samples to uncover somatic genetic changes and especially to look for postzygotic mutations in *PIK3CA*.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

Alexandre Roux, MD, MSc[*‡§]
Miikka Vikkula, MD, PhD[¶]
Johan Pallud, MD, PhD[*‡§]
[*]*Department of Neurosurgery*
GHU Paris
Sainte-Anne Hospital
Paris, France
[‡]*Paris Descartes University*
Sorbonne Paris Cité
Paris, France
[§]*Inserm UMR 1266*
IMA-Brain
Institute of Psychiatry and Neurosciences of Paris
Paris, France
[¶]*Human Molecular Genetics*
de Duve Institute
University of Louvain
Brussels, Belgium

REFERENCES

1. Samuels Y, Wang Z, Bardelli A, et al. High frequency of mutations of the PIK3CA gene in human cancers. *Science*. 2004;304(5670):554.
2. Gallia GL, Rand V, Siu I-M, et al. PIK3CA gene mutations in pediatric and adult glioblastoma multiforme. *Mol Cancer Res*. 2006;4(10):709-714.
3. Osborn AJ, Dickie P, Neilson DE, et al. Activating PIK3CA alleles and lymphangiogenic phenotype of lymphatic endothelial cells isolated from lymphatic malformations. *Hum Mol Genet*. 2015;24(4):926-938.
4. Limaye N, Kangas J, Mendola A, et al. Somatic activating PIK3CA mutations cause venous malformation. *Am J Hum Genet*. 2015;97(6):914-921.
5. Brinjikji W, Hilditch CA, Tsang AC, Nicholson PJ, Krings T, Agid R. Facial venous malformations are associated with cerebral developmental venous anomalies. *AJNR Am J Neuroradiol*. 2018;39(11):2103-2107.
6. Roux A, Edjlali M, Porelli S, et al. Developmental venous anomaly in adult patients with diffuse glioma: a clinically relevant coexistence? *Neurology*. 2019;92(1):e55-e62.
7. Roux A, Boddaert N, Grill J, et al. High prevalence of developmental venous anomaly in diffuse intrinsic pontine gliomas: a pediatric control study. *Neurosurgery*. published online: July 25, 2019 (doi:10.1093/neuros/nyz298).

Acknowledgments

Alexandre Roux would like to thank the Nuovo-Soldati Foundation for Cancer Research for their support.

10.1093/neuros/nyz425