

## ADDENDUM

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**Cancer-associated IDH1 mutations produce 2-hydroxyglutarate**

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This Article demonstrates that tumour-associated IDH1 somatic mutations result in a gain of enzyme function that causes the accumulation of *R*(–)-2-hydroxyglutarate (2HG). We proposed that accumulation of 2HG might drive oncogenesis, and referenced work demonstrating 2HG accumulation in patients with 2-hydroxyglutaric aciduria<sup>1</sup>. As a plausible mechanism of oncogenesis, we proposed that *R*(–)-2HG induces redox stress owing to impairment of the respiratory chain. This hypothesis suggests that *R*(–)-2HG may promote cancer mutations, and is consistent with the latency observed in glioma development and the fact that gliomas increase in incidence with age. Nonetheless, we do appreciate that there are other possible mechanisms by which *R*(–)-2HG may promote tumour formation. Further work has identified that the abnormal production of 2HG is associated with tumours bearing a mutation in either IDH1 or IDH2 and supports a link between 2HG accumulation and cancer. So far, we have not found any tumour samples containing IDH1 or IDH2 mutations that do not have increased 2HG levels. Determining the mechanistic link between 2HG accumulation and cancer formation, and how each stereoisomer of 2HG may drive malignancy by the same or distinct mechanism is the subject of continuing investigation by our group and others.

1. Struys, E. A. *et al.* Mutations in the D-2-hydroxyglutarate dehydrogenase gene cause D-2-hydroxyglutaric aciduria. *Am. J. Hum. Genet.* 76, 358–360 (2005).