Detection of "oncometabolite" 2-hydroxyglutarate by Magnetic Resonance Analysis as a Biomarker of IDH1/2 Mutations in Glioma

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Somatic mutations in isocitrate dehydrogenase *(IDH)1* and *2* have been identified in a subset of gliomas, rendering these tumors with elevated levels of "oncometabolite", D-2-Hydroxyglutarate (2HG). Herein we report that 2HG can be precisely detected by magnetic resonance (MR) in human glioma specimens and used as a reliable biomarker to identify this subset of tumors.

Specifically, using a two-dimensional COrrelation Spectroscopy Resonance (COSY) method we reveal the distinctive cross-peak pattern of 2HG in the complex metabolite nuclear magnetic resonance (NMR) spectra of brain tumor tissues. We show somatic mutations in *IDH1/2* were detected in 37 (57%) of the 65 tumors analyzed, all of which showed elevated levels of 2HG (1-11 mM) by NMR. The levels of 2HG were at (n=1) or below (n=27) the quantification limit (0.1mM) in the 28 mutation-negative tumors and not detectable in all 10 non-tumoral controls. The sensitivity and specificity of detecting 2HG in *IDH1/2* mutation-bearing samples by the 2D COSY reached 96% and 95.2%, respectively. The overall accuracy of identification of *IDH1/2* mutations by NMR using 2HG as a biomarker was 97.8%.

This study demonstrates the feasibility, specificity and selectivity of using MR detection and quantification of 2HG for the diagnosis and classification of *IDH1/2* mutation-positive brain tumors, and further opens up the possibility of developing analogous non-invasive MR-based imaging and spectroscopy studies directly in humans.

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