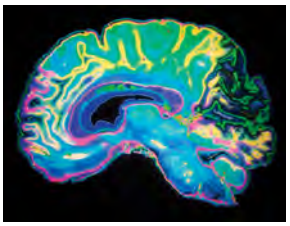
Glioma

Major finding: Magnetic resonance spectroscopy detects 2-hydroxyglutarate in *IDH*-mutant gliomas.

Clinical relevance: Gliomas with *IDH1/2* mutations can be identified without surgical biopsy.

Impact: A surrogate biomarker for *IDH* mutation can improve glioma classification and monitoring.

NONINVASIVE ASSESSMENT OF *IDH* MUTATIONAL STATUS IN GLIOMA



Mutation of the *isocitrate dehydrogenase 1* and *2* (*IDH1/2*) genes frequently occurs in gliomas and results in abnormal accumulation of the metabolite 2-hydroxyglutarate (2HG). It has been proposed that *in vivo* detection of 2HG using magnetic resonance spectroscopy (MRS) could allow noninvasive genotyping of gliomas. However, a major hurdle to detection of 2HG in tumors with conventional 1-dimensional (1D) MRS is the similarity between its chemical structure and that of other metabolites, such as glutamate and glutamine, which are equally abundant in the brain and produce overlapping spectral resonances. To address this problem, spectral editing techniques that isolate relevant spectra and facilitate the specific detection of metabolites have been considered, along with 2D MRS methods capable of separating overlapping resonances. Elkhaled, Jalbert, and colleagues used multiple MRS approaches in their *ex vivo* analysis of image-guided glioma biopsies, establishing that 2HG can be imaged with MRS. An 86.4% concordance was observed between the presence of 2HG, as determined by 1D and 2D high-resolution magic angle spinning spectroscopy, and *IDH1* mutation status as determined by immunohistochemistry and sequencing. The authors also observed that 2HG levels were correlated with histopathologic grade due to increased tumor cellularity. The feasibility of using 2HG as a surrogate biomarker of *IDH* mutation was further established *in vivo* by Andronesi and colleagues, who used spectral editing and 2D MRS techniques to scan the brains of glioma patients with known *IDH1* mutations, glioblastoma patients lacking an *IDH* mutation, and healthy volunteers. Only the spectra of *IDH1*-mutant gliomas, not glioblastomas or healthy controls, contained a peak corresponding to 2HG. Although these results are preliminary, they have the potential to guide stratification of gliomas because *IDH*-mutant gliomas have a better prognosis. This approach may also allow monitoring of the effects of targeted therapies that are being developed to inhibit mutant IDH enzymes. ■

Elkhaled A, Jalbert LE, Phillips JJ, Yoshihara HA, Parvataneni, R, Srinivasan R, et al. Magnetic resonance of 2-hydroxygluturate in IDH1-mutated low-grade gliomas. Sci Transl Med 2012;4:116ra5.

Andronesi OC, Kim GS, Gerstner E, Batchelor T, Tzika AA, Fantin VR, et al. Detection of 2-hydroxyglutarate in IDH-mutated glioma patients by in vivo spectral-editing and 2D correlation magnetic resonance spectroscopy. Sci Transl Med 2012;4:116ra4.

Prostate Cancer

Major finding: *HOXB13* G84E mutation is associated with hereditary prostate cancer risk.

Approach: Linkage analysis and targeted sequencing identified G84E in prostate cancer families.

Impact: Men with early-onset hereditary prostate cancer more frequently carry *HOXB13* G84E.

HOXB13 IS A PROSTATE CANCER SUSCEPTIBILITY GENE

A positive family history is a known risk factor for the development of prostate cancer, but specific germline mutations have not yet been identified. Linkage analyses of families with hereditary disease have pointed to chromosome 17q21-22 as a possible genetic susceptibility locus. Using fine-mapping studies combined with targeted sequencing of 202 genes in this region, Ewing and colleagues found that a mutation in the *HOXB13* gene, resulting in a nonconservative glycine-to-glutamic acid substitution (G84E), is significantly associated with increased risk of hereditary prostate cancer. *HOXB13*, which encodes a transcription factor belonging to the highly conserved homeobox gene family, plays a role in normal prostate development. The G84E variant was identified first in probands from 4 families with hereditary prostate cancer and consequently confirmed in all affected members of these families. Additional genetic analyses revealed a *HOXB13* G84E carrier frequency of 1.4% in men with familial prostate cancer compared with 0.1% in nonaffected controls. Importantly, the highest carrier frequency (3.1%) was found in men with both a positive family history and an early diagnosis of prostate cancer. G84E and 4 other rare *HOXB13* mutations identified in 2 families and 2 prostate cancer cell lines are located in highly conserved functional protein domains. Although the mechanistic role of *HOXB13* G84E in carcinogenesis remains unknown, the findings presented here offer insight into the genetic basis of prostate cancer and may have clinical implications for families with hereditary disease. ■

Ewing CM, Ray AM, Lange EM, Zuhlke KA, Robbins CM, Tembe WD, et al. Germline mutations in HOXB13 and prostate cancer risk. N Engl J Med 2012;366:141–9.