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New Genetic Characteristics of Chondrosarcoma

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Background: Heterozygous mutations of isocitrate dehydrogenase 1 (IDH1) and isocitrate dehydrogenase 2 (IDH2) have recently been identified in cartilaginous neoplasms including conventional central and periosteal cartilage neoplasms. These mutations occur at a single amino acid residue at R132 for IDH1 and R172 and R140 for IDH2. Mutations in these genes lead to impaired ability of IDH1 and IDH2 to catalyze the conversion of isocitrate to alpha ketoglutarate. This results in neomorphic enzymatic activity leading to production of the oncometabolite 2-hydroxyglutarate (2HG). In this study, we analyzed chondrosarcoma for IDH1, IDH2 and other mutations using high-throughput Sequenom-based analysis.

Methods: Chondrosarcomas were genotyped for IDH1 and 2 mutations on the Sequenom Mass Array Platform. In addition, 271 recurrent point mutations across 27 genes were tested as part of the high throughput Sequenom Mass Array Platform panel.

Results: Fifty three chondrosarcomas were selected for the study. There were 30 females and 23 males. The age range was 18 to 77 years with a median of 55 years. Histologically, twenty one (21) were classified as grade I/III, 25 as grade II-III/III and 7 as Dedifferentiated chondrosarcoma. Twenty-six of 53 (50%) patients had mutations in IDH1 or IDH2. No other mutations were detected in the rest of the gene panel (AKT1, AKT2, AKT3, ALK, BRAF, CDK4, CTNNB1, EGFR, ERBB2, FGFR2, FGR3, FLT3, GNAQ, HRAS, JAK2, KIT, KRAS, MAP2K1, MET, NOTCH1, NRAS, PDGFRA, PIK3CA, PIK3R1, PTPN11, RET, SMO) by Sequenom Mass Array spectrometry.

Conclusion:

IDH1 and IDH2 mutations appear to be genetic signatures in half of chondrosarcomas. Downstream effects of these mutations could unravel pathways which could lead to viable therapeutic options. Most common genetic mutations involving genes of the signal transduction pathways do not seem to play a role in the biology of chondrosarcoma.

• Mutations of isocitrate dehydrogenase IDH 1 and IDH 2 occur in one half of chondrosarcomas

• No other candidate genes were mutated in Sequenom analysis.

• Targeting this metabolic pathway promises to be a new strategy to treat chondrosarcoma

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