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Mutational analysis of primary, recurrent and metastatic chordoma tissue using next-generation sequencing

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Background: Chordomas are rare ectodermal bone malignancies that are derived from transformed notochordal remnants. Histologic variants of chordoma include classical (conventional, most common), chondroid (5-15%) and de-differentiated (2-8%). Chordomas are relatively chemotherapy and radiotherapy resistant, and management greatly relies on surgical excision. Novel targeted agents are desperately needed to help expand treatment approaches and improve outcomes.

Questions/Purposes: The primary aim of this study was to analyze the genomic landscape of chordoma across multiple histologic subtypes to identify potential pathogenic and actionable targets.

Methods: 30 tumor samples derived from chordoma patients treated at Massachusetts General Hospital, University of California, Los Angeles, or the University of Miami were included in the study. Primary, recurrent or metastatic chordoma tumor specimens were sent fresh or frozen for comprehensive molecular profiling using next-generation sequencing (NGS) technology with the following platforms: Foundation (18), GPS (1), Caris (3), SnAPshot (3), Tempus (4) and Intermountain genomics (1). Most frequently mutated genes, tumor mutational burden and micro-satellite instability data were categorized into tumor subtype and tissue source.

Results: Histologic subtypes included: 20 conventional chordomas, 5 chondroid chordomas and 5 de-differentiated chordomas. 23 samples were annotated to source, with 3 derived from primary tumor, 9 from recurrent tumor and 11 from metastatic tumors. The most common gene mutations identified were: CDKN2A or 2B (13/30, 43%), EGFR (5/30, 17%), LRP1B (5/30, 17%) and BRCA1 or 2 (3/30, 10%). By sub-type, CDKN2A/B (coding for p16(INK4A) protein, binding and blocking CDK4's or CDK6's ability to stimulate cell cycle progression) mutation was most common in conventional chordoma (11/20, 55%), and chondroid chordoma (2/5, 40%), while EGFR (2/5, 40%) mutations were most common in de-differentiated chordoma. Mean identified mutations were 5.5/sample in conventional chordomas (range 1-15), 4.2/samples in chondroid chordoma (1-11) and 11.8/sample in de-differentiated chordoma (4-25). Microsatellite instability was absent in 3/3 conventional chordoma samples. Tumor mutational burden (m/Mb) was available for 1 primary (1 m/Mb), 2 recurrent (4.1 m/Mb) and 1 metastatic (2.1 m/Mb) sample.

Conclusions: These data provide a robust high-dimensional sequencing assessment from 30 chordoma tissue samples, providing a descriptive overview of the genomic landscape of this rare, difficult to treat malignancy. Further clinical sample annotation is underway, including validation using tissue microarray analysis of primary chordoma samples. Future studies should also include *in vitro* assessment and of gain and loss of function of frequently altered pathways such as CDKN2A/B (p16/CDK4/6), EGFR, LRP1B and BRCA1/2.