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Report

Recurrent Somatic Structural Variations Contribute to Tumorigenesis in Pediatric Osteosarcoma

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SUMMARY

Pediatric osteosarcoma is characterized by multiple somatic chromosomal lesions, including structural variations (SVs) and copy number alterations (CNAs). To define the landscape of somatic mutations in pediatric osteosarcoma, we performed whole-genome sequencing of DNA from 20 osteosarcoma tumor samples and matched normal tissue in a discovery cohort, as well as 14 samples in a validation cohort. Single-nucleotide variations (SNVs) exhibited a pattern of localized hypermutation called kataegis in 50% of the tumors. We identified p53 pathway lesions in all tumors in the discovery cohort, nine of which were translocations in the first intron of the *TP53* gene. Beyond *TP53*, the *RB1*, *ATRX*, and *DLG2* genes showed recurrent somatic alterations in 29%–53% of the tumors. These data highlight the power of whole-genome sequencing for identifying recurrent somatic alterations in cancer genomes that may be missed using other methods.

INTRODUCTION

Osteosarcoma is the most common malignant bone tumor in children and adolescents, with approximately 400 new cases each year in the United States (Ottaviani and Jaffe, 2009). Although most cases are sporadic, the risk of osteosarcoma is increased in patients with various genetic diseases, including hereditary retinoblastoma, Li Fraumeni syndrome, and germline mutations of *RecQL4* (Hicks et al., 2007; Kleinerman et al., 2005; McIntyre et al., 1994). Current multimodal therapies that incorporate surgical excision and combination chemotherapy (i.e., doxorubicin, methotrexate, and cisplatin) cure approximately 70% of patients (Meyers et al., 2005). However, clinical outcomes and therapeutic strategies have remained virtually unchanged over the past 20 years (Smith et al., 2010).

In this study, we characterized the genomic landscape of osteosarcoma by performing whole-genome sequencing (WGS) on 34 osteosarcoma tumor and matched nontumor tissue samples from 32 patients. Our results demonstrate that pediatric osteosarcomas have one of the highest rates of SVs of any pediatric cancer sequenced to date (Downing et al., 2012), but relatively few recurrent single-nucleotide variations (SNVs). However, when SVs and SNVs were combined, inactivating mutations were identified in several cancer pathways. Taken together, our results provide insights into the molecular pathology of pediatric osteosarcoma and demonstrate that comprehensive WGS is required to elucidate the complete genetic landscape of osteosarcoma.

RESULTS

WGS of Primary and Metastatic Osteosarcomas

Using a paired-end sequencing approach, we generated 10,265 Gb of sequence data for DNA in 20 osteosarcomas and matched

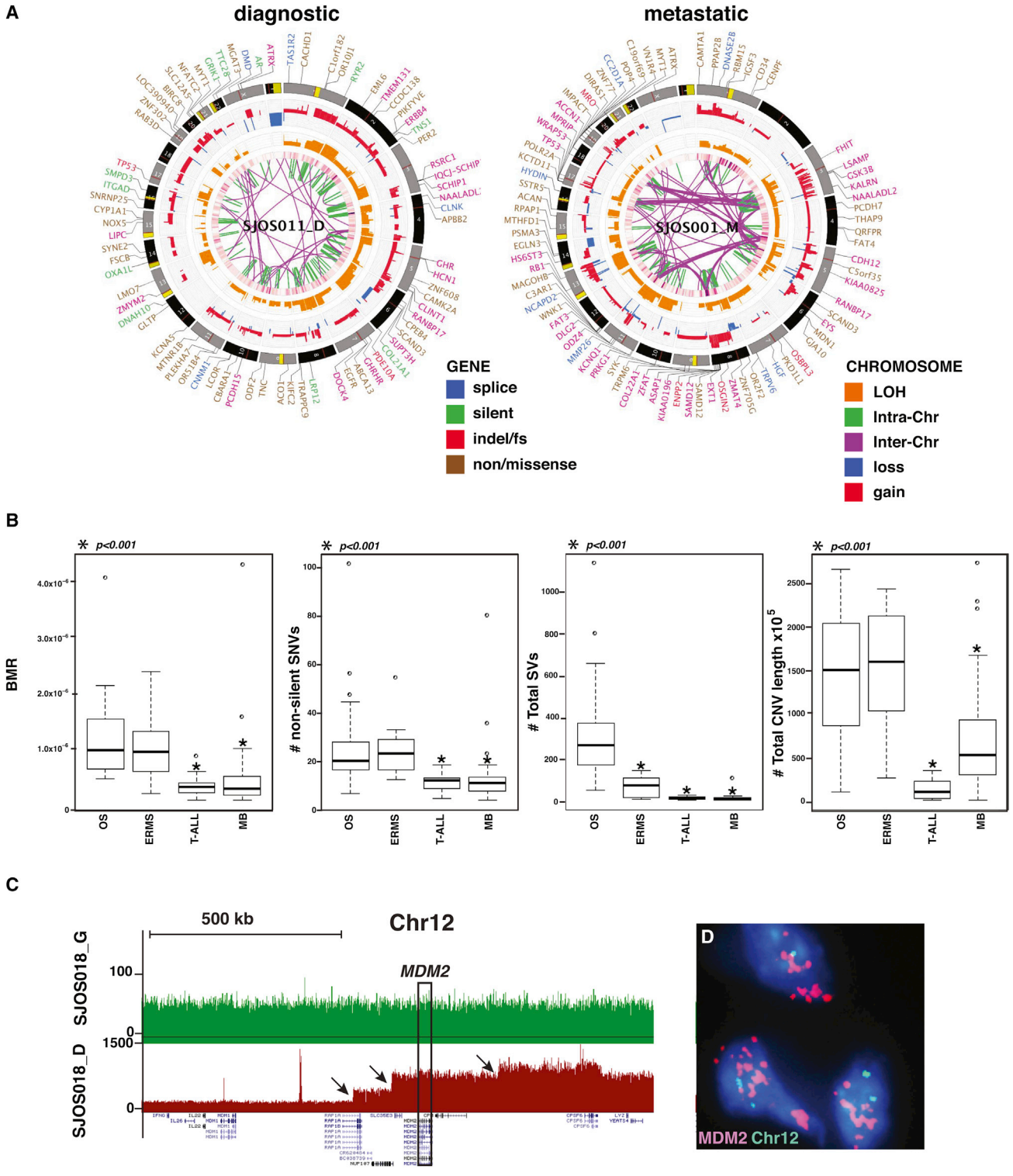

Figure 1. WGS of Osteosarcoma

(A) Representative CIRCOS plots of validated mutations and chromosomal lesions in diagnostic and metastatic osteosarcoma tumors from different patients. LOH (orange), gain (red), and loss (blue) are shown. Intrachromosomal (green lines) and interchromosomal (purple lines) translocations are indicated. Sequence mutations in RefSeq genes included silent SNVs (green), nonsense and missense SNVs (brown), splice-site mutations (dark blue), and insertion/deletion mutations (red). An additional track was added to the innermost ring of the plot showing the density of SNVs to highlight regions adjacent to SVs characteristic of kataegis.

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