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The Architecture and Evolution of Cancer Neochromosomes

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SUMMARY

We isolated and analyzed, at single-nucleotide resolution, cancer-associated neochromosomes from well- and/or dedifferentiated liposarcomas. Neochromosomes, which can exceed 600 Mb in size, initially arise as circular structures following chromothripsis involving chromosome 12. The core of the neochromosome is amplified, rearranged, and corroded through hundreds of breakage-fusion-bridge cycles. Under selective pressure, amplified oncogenes are overexpressed, while coamplified passenger genes may be silenced epigenetically. New material may be captured during punctuated chromothriptic events. Centromeric corrosion leads to crisis, which is resolved through neocentromere formation or native centromere capture. Finally, amplification terminates, and the neochromosome core is stabilized in linear form by telomere capture. This study investigates the dynamic mutational processes underlying the life history of a special form of cancer mutation.

Significance

Different cancers reveal distinct mutation patterns, from mismatch repair defects in colorectal cancers to translocations that generate fusion genes in subtypes of leukemia. Neochromosomes are a form of mutation comprising the somatic acquisition of massive, episomal, self-replicating structures within cancer cells, specific to certain cancer types, including several sarcomas. We describe, at single-nucleotide level, the structure and content of well- and/or dedifferentiated liposarcoma neochromosomes, and we used mathematical modeling to understand their origins and oncogenic properties.

INTRODUCTION

Chromosomes are a fundamental organizational unit of genetic information relevant to biology and disease. Contiguous sequences of circular or linear DNA and associated proteins from 0.1 Mb to 1 Gb in length (Paux et al., 2008), all nuclear chromosomes require centromeres and, when in linear form, telomeres (Baird and Farr, 2006). In humans, in addition to 46 normal

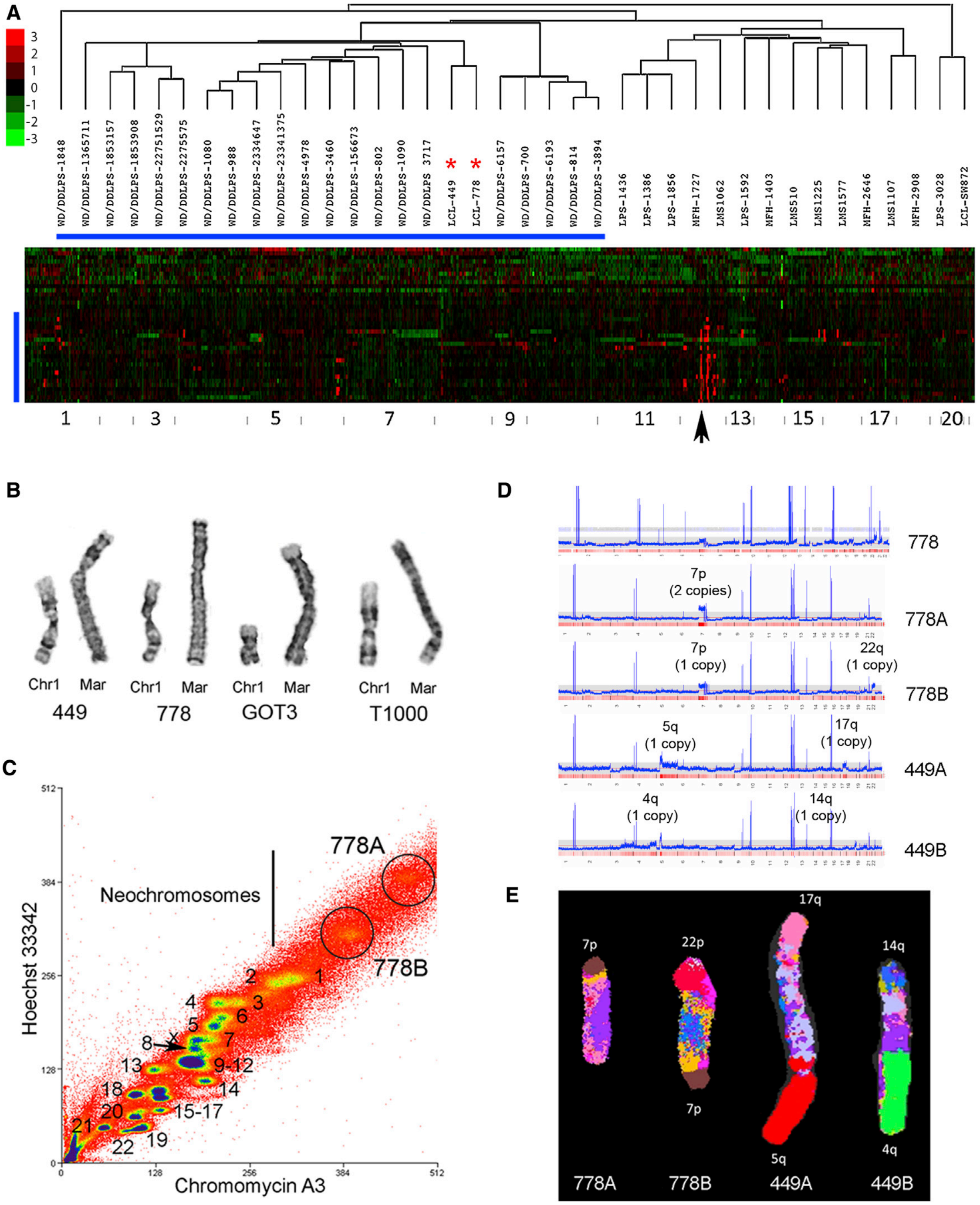

Figure 1. Characterization and Analysis of WD/DDLPS Cell Lines

(A) Hierarchical clustering of bacterial artificial chromosome array-based comparative genomic hybridization of 21 primary WD/DDLPSs, 5 pleomorphic liposarcomas (LPS), 4 undifferentiated pleomorphic sarcomas (MFH), and 5 leiomyosarcomas (LMS), as well as the 778 and 449 (indicated by stars) and SW872 cell lines (LCL). In the heatmap, rows represent samples, and columns represent probes. Beneath the dendrogram is the corresponding copy number heatmap (in landscape orientation). Heatmap color indicates the $\log_2$ copy number ratio (normal, $\log_2 = 0$); amplifications are red, and deletions are green. Blue bars demarcate WD/DDLPS samples and cell lines. The arrowhead marks the defining amplification of regions from chromosome 12q.

(B) G-banded marker neochromosomes from the 778, 449, GOT3, and T1000 cell lines, compared to chromosome 1 (Chr1).

(C) Representative flow dot plot of chromosomes from the 778 cell lines, showing the position of normal chromosomes as well as two marker neochromosome populations (circled). Chromosomes were stained for flow sorting with the fluorescent DNA-intercalating dyes as shown.

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