TP53 intron 1 hotspot rearrangements are specific to sporadic osteosarcoma and can cause Li-Fraumeni syndrome.

Somatic mutations of TP53 are among the most common in cancer and germline mutations of TP53 (usually missense) can cause Li-Fraumeni syndrome (LFS). Recently, recurrent genomic rearrangements in intron 1 of TP53 have been described in osteosarcoma (OS), a highly malignant neoplasm of bone belonging to the spectrum of LFS tumors. Using whole-genome sequencing of OS, we found features of TP53 intron 1 rearrangements suggesting a unique mechanism correlated with transcription. Screening of 288 OS and 1,090 tumors of other types revealed evidence for TP53 intron 1 rearrangements in 46 (16%) OS, while none were detected in other tumor types, indicating this rearrangement to be highly specific to OS. We revisited a four-generation LFS family where no TP53 mutation had been identified and found a 445 kb inversion spanning from the TP53 intron 1 towards the centromere. The inversion segregated with tumors in the LFS family. Cancers in this family had loss of heterozygosity, retaining the rearranged allele and resulting in TP53 expression loss. In conclusion, intron 1 rearrangements cause
p53-driven malignancies by both germline and somatic mechanisms and provide an important mechanism of TP53 inactivation in LFS, which might in part explain the diagnostic gap of formerly classified "TP53 wild-type" LFS.