Fusion and rearrangement (RE) detection using DNA and RNA-based comprehensive genomic profiling (CGP) of sarcomas

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BACKGROUND

Actionability of a growing subset of gene fusions and rearrangement (RE) is well established, with several alterations linked to approved targeted therapies. While there are FDA-approved assays for DNA-based detection of key recurring actionable RE sarcomas can be enriched for rare RE not comprehensively covered on DNA panels.

METHODS

- DNA and RNA comprehensive genomic profiling (CGP; FoundationOneHeme®) was performed on 9,969 sarcoma tissue specimens
- DNA and RNA was co-extracted from up to1.2 mm^3 of FFPE tissue.
- Adaptor ligation-based hybrid capture-based sequencing was performed for up to 406 cancer-related genes and select introns from 28 genes commonly rearranged in cancer, and 265 RNA fusion genes.
- Mean coverage depth was >600X
- Base substitutions, insertions and deletions (short variants; SV), rearrangements, and copy number changes were assessed
- Actionable genes: *NTRK1/2/3, BRAF MET, ALK, ERBB2, EGFR, FGFR1/2/3*, *ROS1*, *RET, NRG1*
- Diagnostic genes/fusions: *EWSR1*, *STAT6-NAB2*, *BCOR-ZC3H7B*, *BCOR-CCNB3*, *FOXO1-PAX3/7*
- *ALK* fusions with breakpoints in intron 18, exon 19, or intron 19 were considered canonical
- Rearrangements where DNA detected a non-fusion and RNA detected a fusion were classified as “DNA resolved by RNA”
- DNA breakpoints detected outside of baited regions are due to incidental coverage from fully baited areas or baiting of the partner gene.

RESULTS

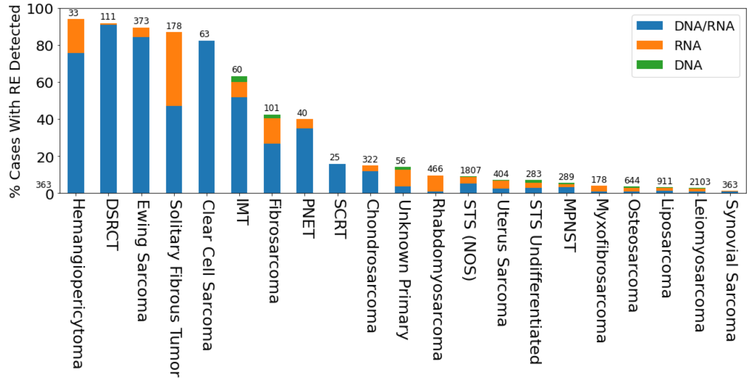

Figure 1: Most sarcoma RE were detected in both DNA and RNA. Exceptions are seen for fusions with rare breakpoints not covered by DNA baiting, particularly in hemangiopericytomas, solitary fibrous tumors, and rhabdomyosarcomas. Total cases indicated by bar label

RESULTS

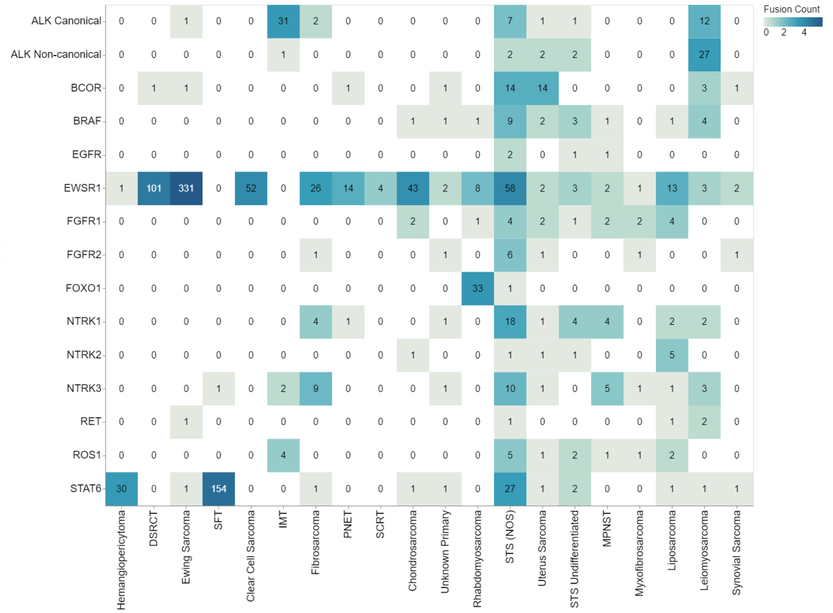

Figure 2: Diverse fusions are seen across a wide range of sarcomas

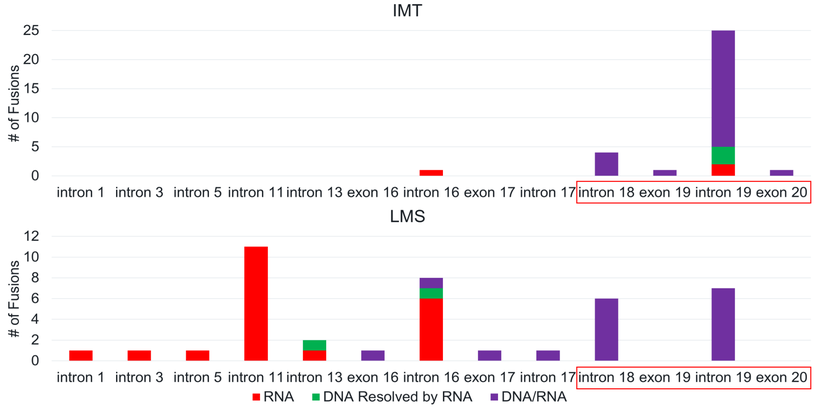

Figure 3: IMTs typically harbor canonical *ALK* fusions which are detected in by DNA and RNA while non-canonical *ALK* fusions in LMS are frequently detected with RNA only. Breakpoints covered by DNA baiting are in red boxes.

RESULTS

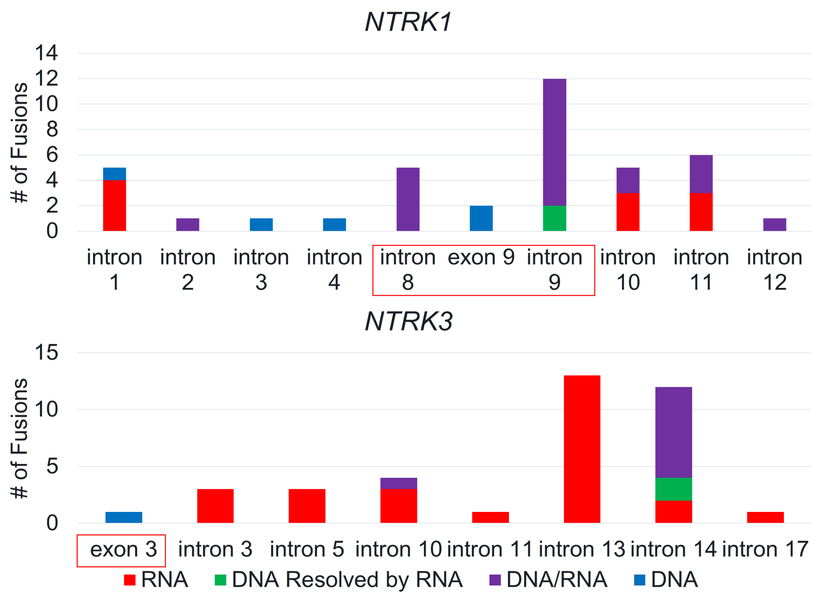

Figure 4: Of 36 *NTRK1/3* fusions detected in DNA (6 DNA only; 30 DNA + RNA), 79% were confirmed in RNA. An additional 37 fusions were detected in RNA only, 100% were outside of the DNA baited region (*NTRK1* intron 7, 8, & 9; *NTRK3* no intron baiting) Breakpoints covered by DNA baiting are in red boxes.

CONCLUSIONS

- In most cases rearrangements were detected in both DNA/RNA.
- 96% (882/914) of all fusions detected in DNA were confirmed in RNA.
- 25% (316/1271) of fusions were only detected in RNA and 3% (41/1271) had complex DNA rearrangements resolved by RNA. RNA baiting increased the sensitivity for atypical fusions with noncanonical breakpoints which may not be covered by DNA baiting.
- For *ALK* and *NTRK1/3* non-fusion DNA rearrangements, RNA further resolved the event: either an actionable RNA fusion was detected, or no RNA event was observed to support the actionability of the DNA finding

Disclosures: KG was a member of the Foundation Medicine, Inc. Advisory Board
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