A066 · Comprehensive cancer transcriptome analysis reveals lncRNA-derived gene fusions as a widespread class of recurrent alterations with oncogenic potential

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Session: Day 2 · Fri Oct 2, 2026 · 2:15–4:15 PM

Gene fusions are pivotal drivers of oncogenesis, yet the contribution of long noncoding RNAs (lncRNAs) to the fusion landscape remains largely unexplored due to the limitations of standard gene annotation-dependent identification pipelines. Here, we performed a comprehensive cancer transcriptome analysis to systematically identify the landscape of lncRNA-derived gene fusions (lncRNA-fusions) using neuroblastoma as a model system characterized by extensive structural variation and biological heterogeneity. By developing and utilizing LncFusion, an integrative computational framework that couples de novo lncRNA discovery with consensus fusion calling, we identified 1,491 high-confidence fusions across 515 tumors. LncRNA-fusions accounted for approximately 60% of detected fusions. Comparative analyses revealed that lncRNA-fusions exhibit significantly higher recurrence than canonical mRNA::mRNA fusions and frequently dominate the fusion landscape within individual tumors. These alterations arise through both chromosomal rearrangements and transcriptional splicing mechanisms, and integrate into oncogenic networks involving established drivers such as MYC, MYCN, and ALK. Integrative prioritization identified six highly recurrent lncRNA-fusions as candidate drivers, including HERC2::HSALNG0104782, which is associated with genomic instability and poor survival. Collectively, this study reveals lncRNA-fusions as a widespread and clinically relevant class of recurrent alterations with oncogenic potential and provides a broadly applicable analytical framework for uncovering noncoding fusion events in cancer.

Comprehensive cancer transcriptome analysis reveals lncRNA-derived gene fusions as a widespread class of recurrent alterations with oncogenic potential

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ABSTRACT
Gene fusions are pivotal drivers of oncogenesis, yet the contribution of long noncoding RNAs (lncRNAs) to the fusion landscape remains largely unexplored due to the limitations of standard gene annotation-dependent identification pipelines. Here, we performed a comprehensive cancer transcriptome analysis to systematically identify the landscape of lncRNA-derived gene fusions (lncRNA-fusions) using neuroblastoma as a model system characterized by extensive structural variation and biological heterogeneity. By developing and utilizing *LncFusion,* an integrative computational framework that couples *de novo* lncRNA discovery with consensus fusion calling, we identified 1,491 high-confidence fusions across 515 tumors. LncRNA-fusions accounted for approximately 60% of detected fusions. Comparative analyses revealed that lncRNA-fusions exhibit significantly higher recurrence than canonical mRNA::mRNA fusions and frequently dominate the fusion landscape within individual tumors. These alterations arise through both chromosomal rearrangements and transcriptional splicing mechanisms, and integrate into oncogenic networks involving established drivers such as *MYC*, *MYCN,* and *ALK*. Integrative prioritization identified six highly recurrent lncRNA-fusions as candidate drivers, including *HERC2::HSALNG0104782*, which is associated with genomic instability and poor survival. Collectively, this study reveals lncRNA-fusions as a widespread and clinically relevant class of recurrent alterations with oncogenic potential and provides a broadly applicable analytical framework for uncovering noncoding fusion events in cancer.

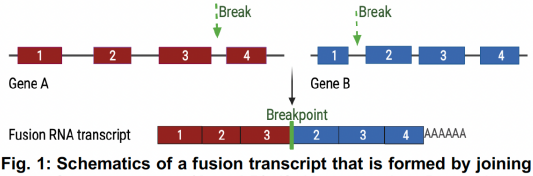

Fig. 1: Schematics of a fusion transcript that is formed by joining exons from two genes (A and B). If either gene A or B encodes an lncRNA, this fusion transcript is an lncRNA-involved fusion (lncRNA-fusion). Boxes represent exons, and lines connecting the boxes are introns. The joint region within the fusion is called a breakpoint.