Preliminary FusionSeq Analysis of Kidney Cancer

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FusionSeq analysis of 33 RNA-seq samples

Got FusionSeq to work with GENCODE19 annotations

Module 1 (detecting fusions)
227131 unique events

Module 2 (filtering spurious fusions)
10 confident events (reduced from 246)

Issues with annotations on pseudogenes/immune proteins

Fusion Genes	Type	Number of samples
ACTB - NXPE1	trans (chr7-chr11)	10
NXPE1-ACTB	trans (chr7-chr11)	5
NOTCH2-PHKB	trans (chr1-chr16)	4
TIMM13-LMNB2	read-through (chr19)	4
LMNB2-TIMM13	read-through (chr19)	4
OARD1-UNC5L	read-through (chr6)	2
BIVM-ERCC	read-through (known - chr13)	2
PID1 and RP11-60A24	trans (chr2-chr17)	1
PHKB-NOTCH2	trans (chr16-chr1)	1
ERCC-BIVM	read-through (known - chr13)	1

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Novel MIR143-NOTCH Fusions in Benign and Malignant Glomus Tumors

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Glomus tumors (GT) have been classified among tumors of perivascular smooth muscle differentiation, together with myopericytoma, myofibroma/tosis, and angioleiomyoma, based on their morphologic overlap. However, no molecular studies have been carried out to date to investigate their genetic phenotype and to confirm their shared pathogenesis. RNA sequencing was performed in three index cases (GT1, malignant GT; GT2, benign GT and M1, multifocal myopericytoma), followed by FusionSeq data analysis, a modular computational tool developed to discover gene fusions from paired-end RNA-seq data. A gene fusion involving *MIR143* in band 5q32 was identified in both GTs with either *NOTCH2* in 1p13 in GT1 or *NOTCH1* in 9q34 in GT2, but none in M1. After being validated by FISH and RT-PCR, these abnormalities were screened on 33 GTs, 6 myopericytomas, 9 myofibroma/toses, 18 angioleiomyomas and in a control group of 5 sino-nasal hemangiopericytomas. Overall *NOTCH2* gene rearrangements were identified in 52% of GT, including all malignant cases and one NF1-related GT. No additional cases showed *NOTCH1* rearrangement. As NOTCH3 shares similar functions with NOTCH2 in regulating vascular smooth muscle development, the study group was also investigated for abnormalities in this gene by FISH. Indeed, *NOTCH3* rearrangements were identified in 9% of GTs, all present in benign soft tissue GT, one case being fused to *MIR143*. Only 1/18 angioleiomyomas showed *NOTCH2* gene rearrangement, while all the myopericytomas and myofibroma/toses were negative. In summary, we describe novel *NOTCH1–3* rearrangements in benign and malignant, visceral, and soft tissue GTs.

NOTCH2 fusions are found often in breast, and glomus cancer.

NOTCH2 mutations are known to be associated with kidney cancer too.

NOTCH2 is a signaling protein and PKB is phosphokinase protein.

Need to do breakpoint analysis for transcript fusion!

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PRECLINICAL STUDY

Recurrent read-through fusion transcripts in breast cancer

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Abstract Read-through fusion transcripts that result from the splicing of two adjacent genes in the same coding orientation are a recently discovered type of chimeric RNA. We sought to determine if read-through fusion transcripts exist in breast cancer. We performed paired-end RNA-seq of 168 breast samples, including 28 breast cancer cell lines, 42 triple negative breast cancer primary tumors, 42 estrogen receptor positive (ER+) breast cancer primary tumors, and 56 non-malignant breast tissue samples. We analyzed the sequencing data to identify breast cancer associated read-through fusion transcripts. We discovered two recurrent read-through fusion transcripts that were identified in breast cancer cell lines, confirmed across breast cancer primary tumors, and were not detected in normal tissues (*SCNN1A-TNFRSF1A* and *CTSD-IFITM10*). Both fusion transcripts use canonical splice sites to join the last splice donor of the 5′ gene to the first splice acceptor of the 3′ gene, creating an in-frame fusion transcript. Western blots indicated that the fusion transcripts are translated into fusion proteins in breast cancer cells. Custom small interfering RNAs targeting the *CTSD-IFITM10* fusion junction reduced expression of the fusion transcript and reduced breast cancer cell proliferation. Read-through fusion transcripts between adjacent genes with different biochemical functions represent a new type of recurrent molecular defect in breast cancer that warrant further investigation as potential biomarkers and therapeutic targets. Both breast cancer associated fusion transcripts identified in this study involve membrane proteins (*SCNN1A-TNFRSF1A* and *CTSD-IFITM10*), which raises the possibility that they could be breast cancer-specific cell surface markers.

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Breast cancer-specific recurrent read-through transcripts in membrane proteins.

TIMM13-LMNB2 are membrane proteins.

New module - Under development

Knowledge driven fusion transcript discovery

SV from WGS

Confident transcripts from other samples

Literature