Driver Kinase Fusions in Cancer

TCGA 4th Annual Scientific Symposium – May 12th, 2015

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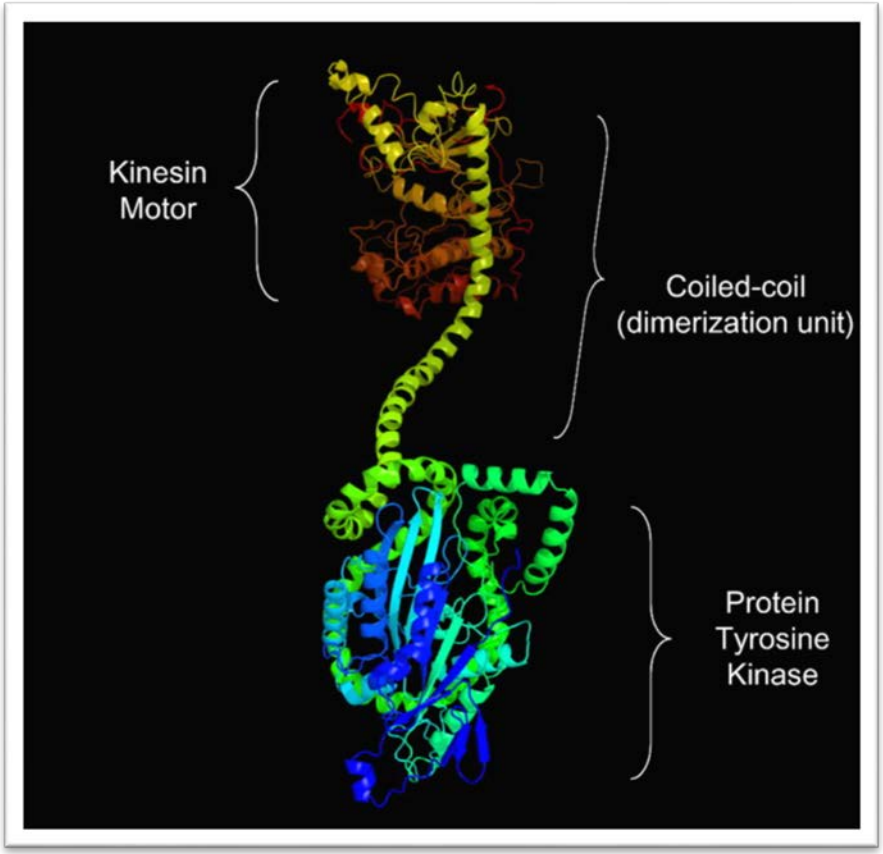
What are Kinase Fusions?

- Genomic instability, a hallmark of cancer, can result in chromosomal translocations or other complex rearrangements
- These events can produce chimeric genes called “fusions”
- Known driver kinase events include *BCR-ABL1* in CML, *EML4-ALK* in Lung adenocarcinoma

KIF5B-RET Fusion



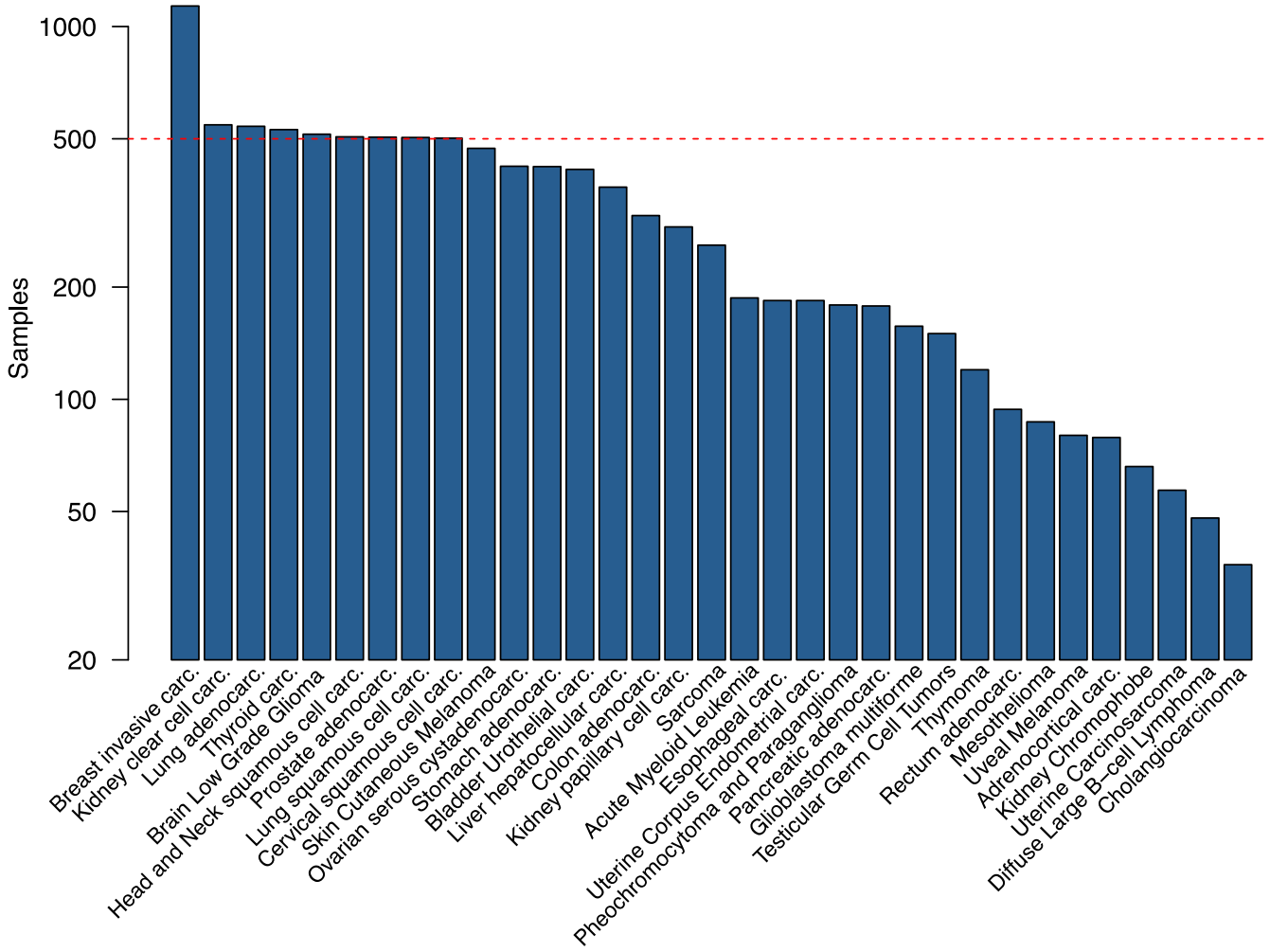
Ju Y S *et al*. Genome Res. 2012

May 2015:
>10,000 RNAseq Samples in TCGA, 33 Tumor Types

TCGA RNA-seq data for ~10,000 tumors

Fusion finding algorithm

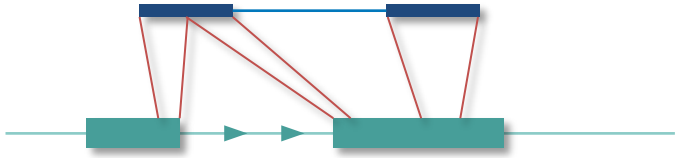
First pan-cancer evaluation of fusions



Novel Algorithm for Rapid Kinase Gene Fusion Detection

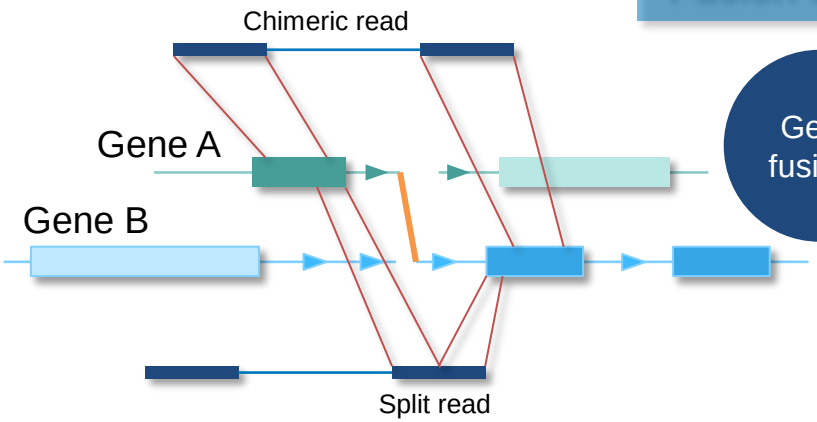
RNA-seq raw reads

Fast alignment



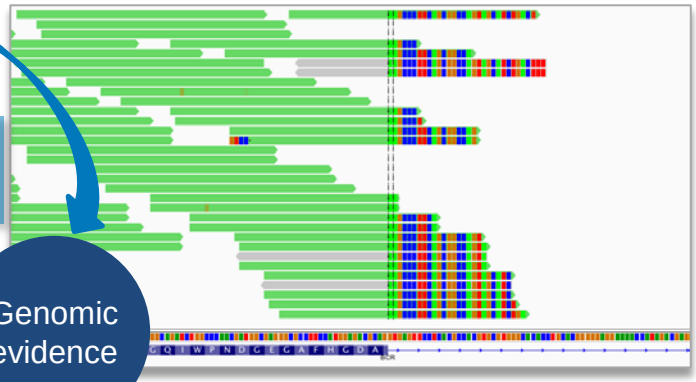
Aligned reads (bam)

Fusion detection



Gene fusions

Isolation of supporting reads



Genomic evidence

- Optimized for sensitivity and speed
- Large speed improvement over public algorithms
- Real-time analysis of new data (TCGA, ICGC, Blueprint data)

Computational Pipeline for Fusion Detection

Fusion Detection

- Core algorithm
  - Identifies gene-gene fusions in RNA-seq data
  - Reports supporting evidence for each fusion

Post-processing

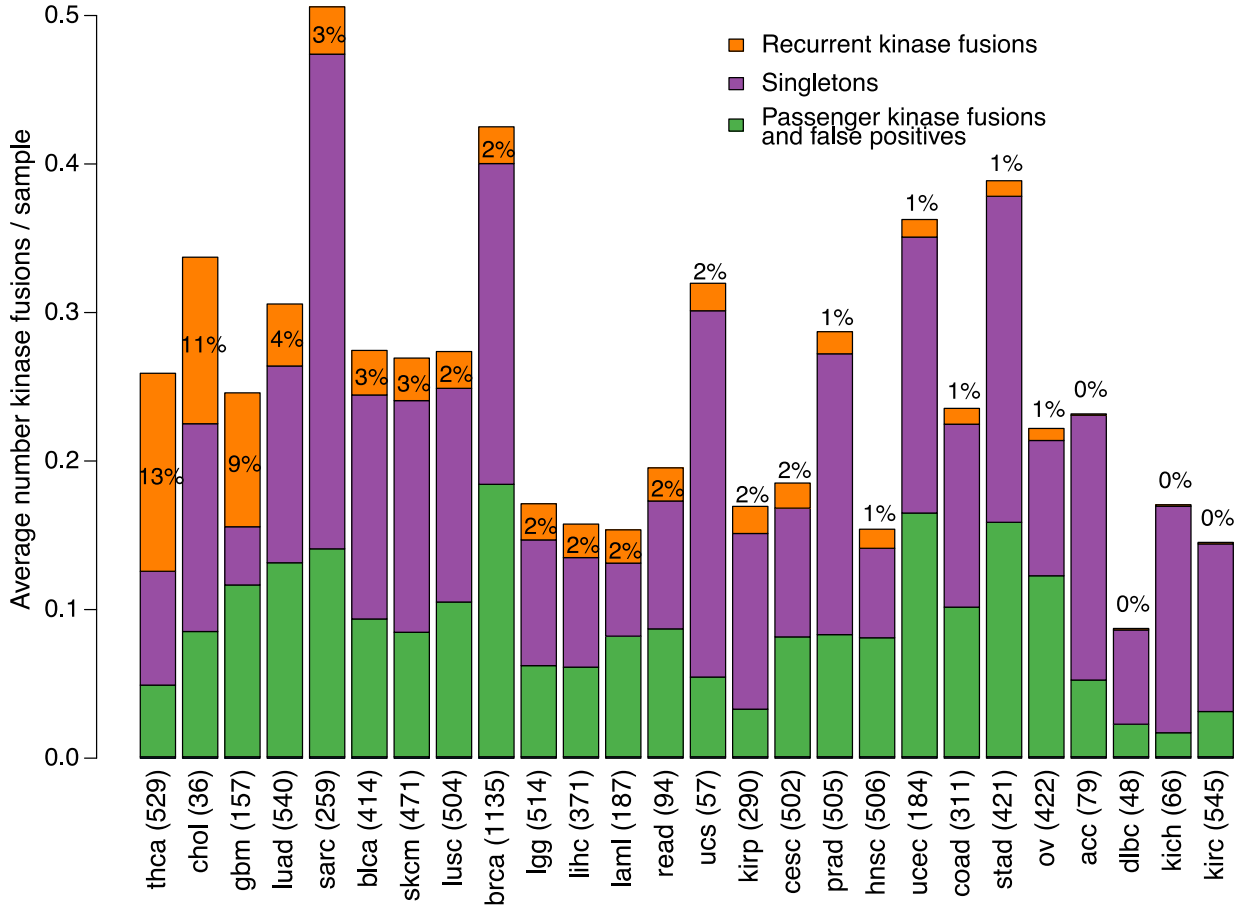
- Post-processing
  - Heuristics to filter out passenger events
    - Intergenic junctions (between two exons)
    - Coding sequence in frame
    - **Presence of kinase catalytic domain**
  - Heuristics to filter out false-positives
    - Fusions present in normal
    - Alignment artifacts (repetitive sequences)
    - High expression level of one partner

Therapeutic relevance

- Reporting tools
  - Reporting of pipeline outputs, fusion frequencies
  - Manually review and annotate fusions

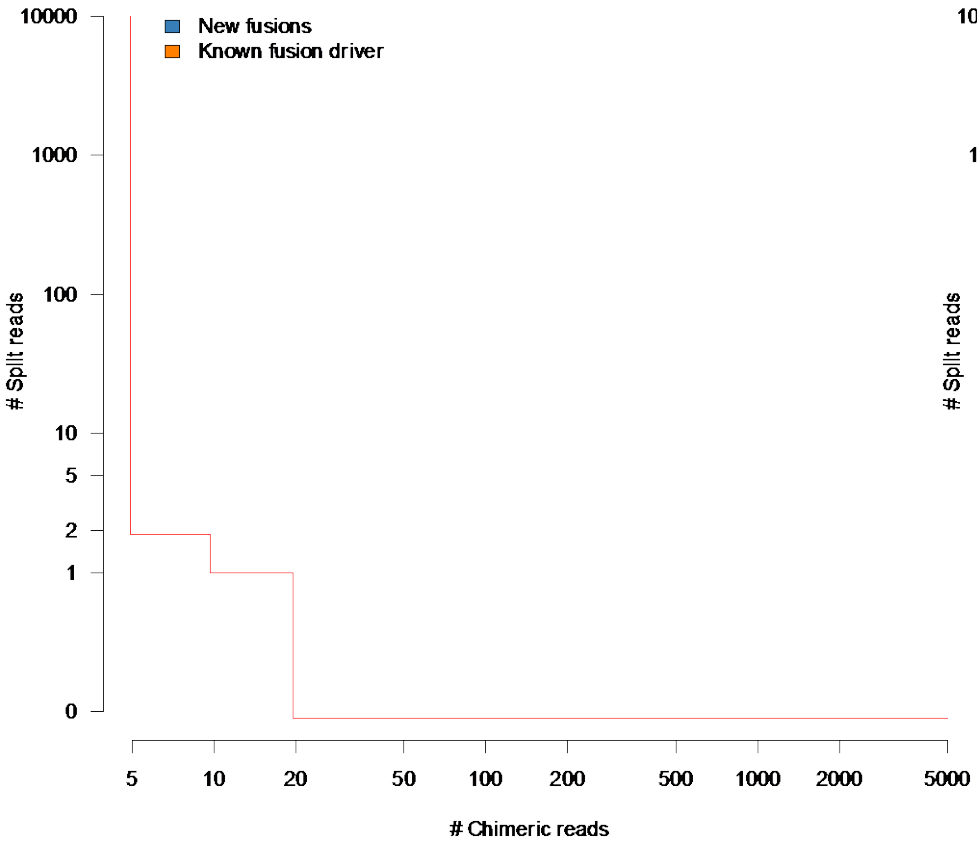
Stransky *et al.* Nature Communications, 2014

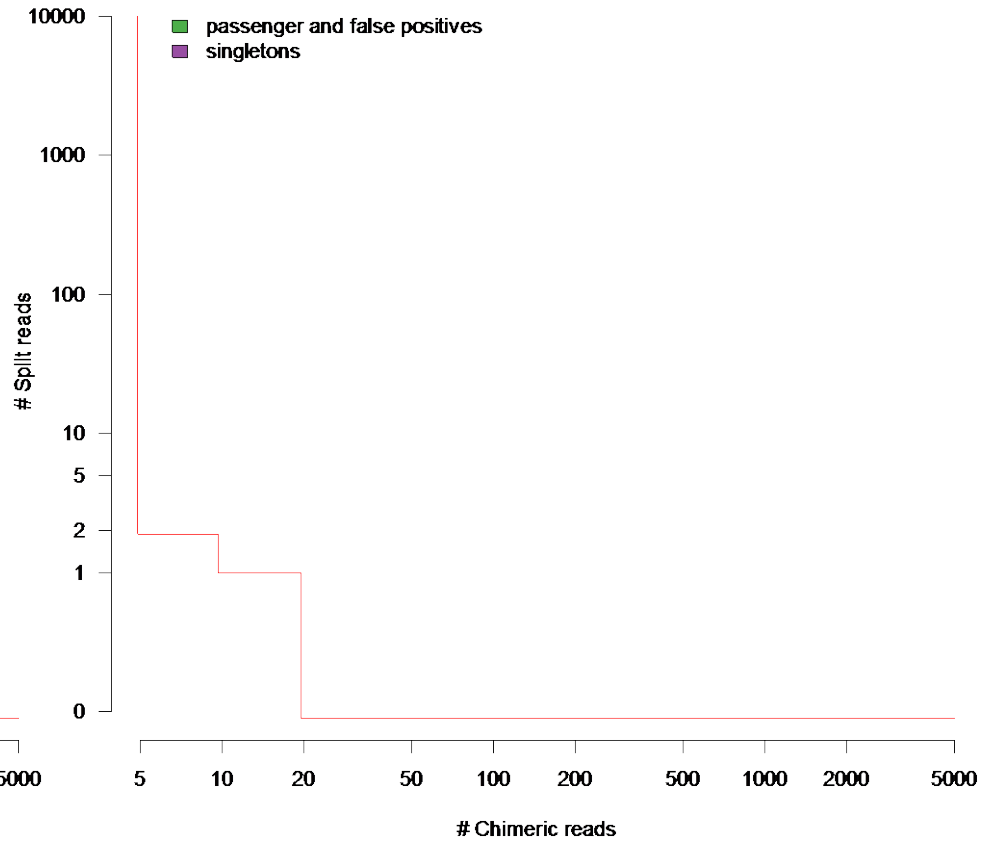
Pipeline output: kinase fusions after manual review



- 2.8 % of tumor samples contain a likely oncogenic kinase fusion (2.0 % excluding thyroid cancer)
- Thyroid cancer, sarcoma and glioblastoma have the highest proportion of recurrent kinase fusions
- Kidney clear cell and kidney chromophobe have almost no kinase fusions

Genomic evidence for novel kinase fusion events

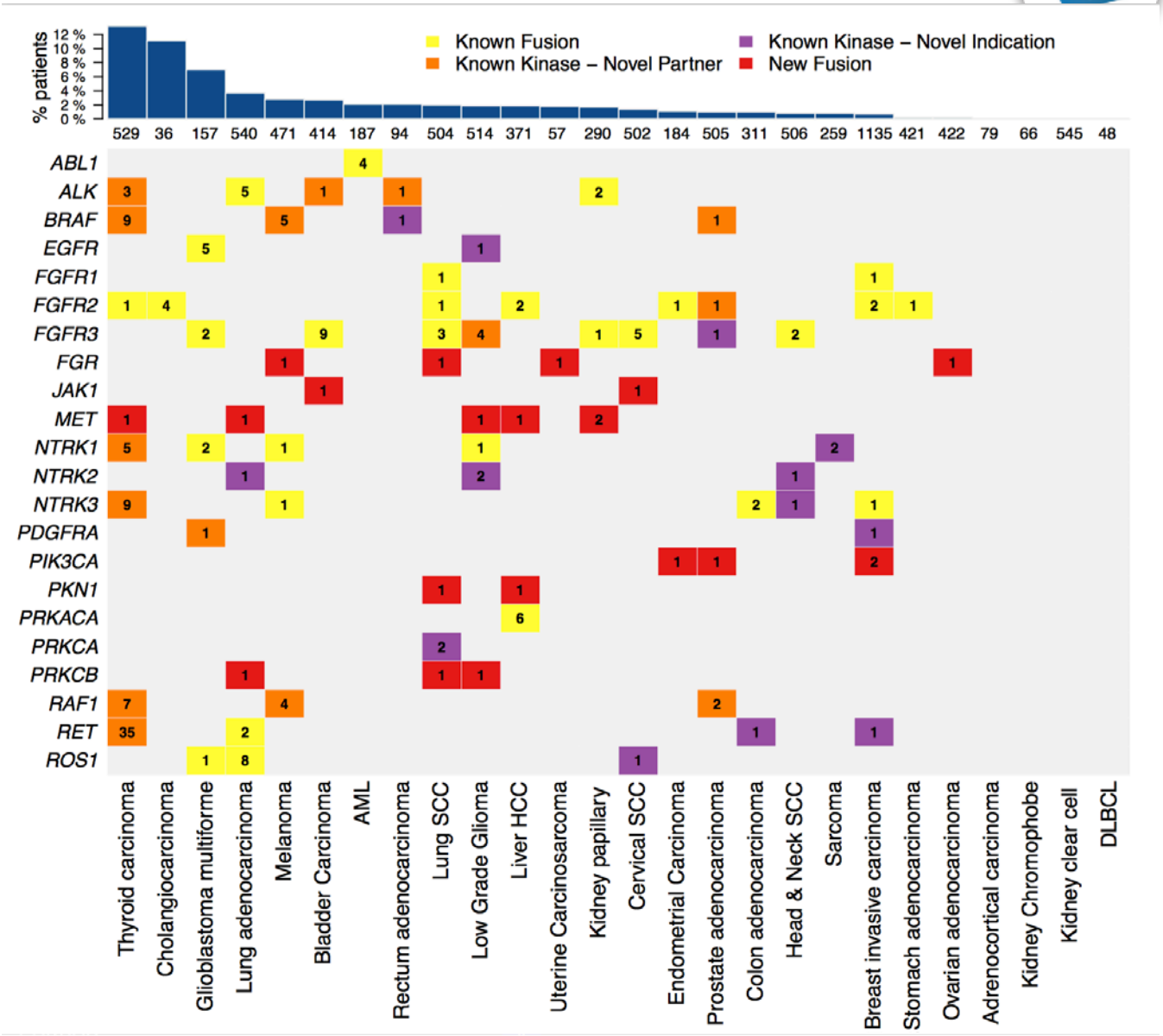




The Landscape of Kinase Fusions in Cancer

New Indications and New Gene Partners

Novel Recurrent Kinase Fusions

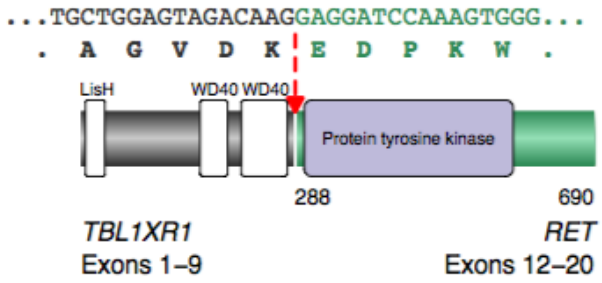


Adapted from Stransky *et al.*
Nature Communications, 2014

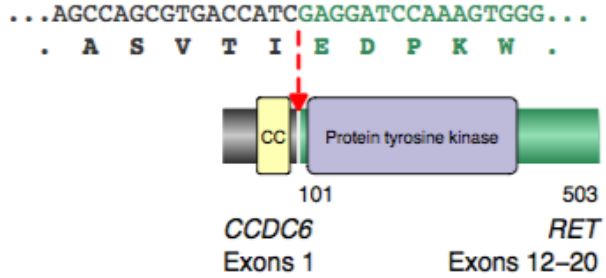
Novel partners and novel indications for kinase fusions

RET

participant ID: 47ad3d2e-9096-4e6d-884f-83507fd8e970
cancer type: thyroid carcinoma

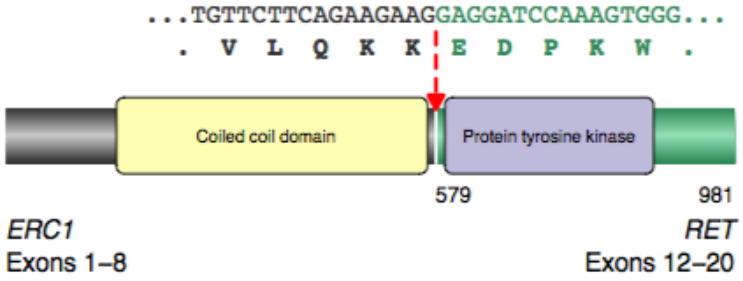


participant ID: c8d7eb0f-2502-4277-a8ef-435b08f3c863
cancer type: colon adenocarcinoma



Known partners

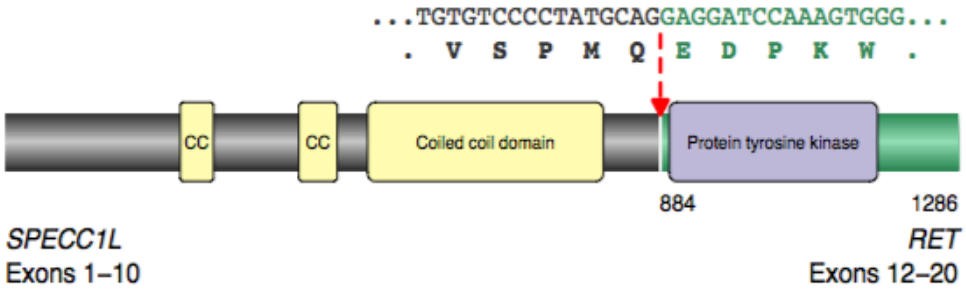
participant ID: 8a209c68-bef9-4191-b6ec-7a1a9258b3bd
cancer type: breast invasive carcinoma



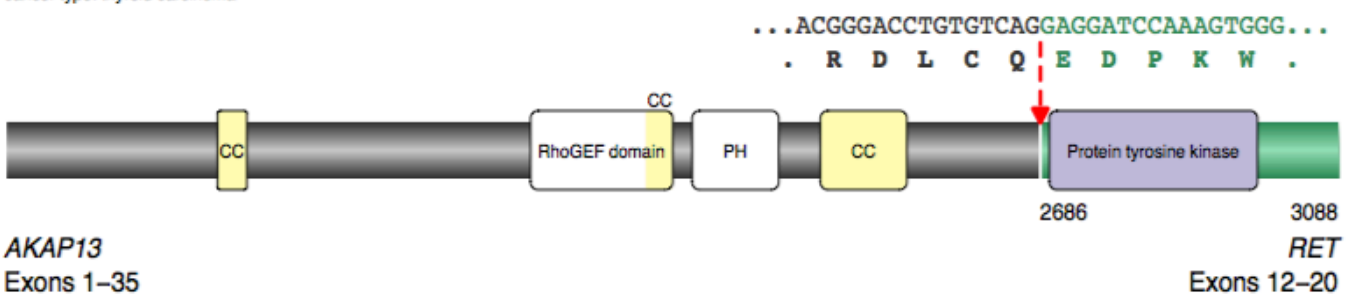
Novel partners and novel indications for kinase fusions

RET

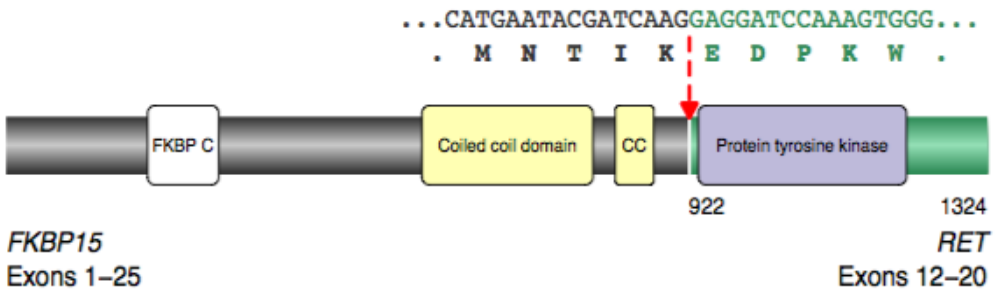
participant ID: 3d114411-0215-4870-87d6-7ff08ca8f771
cancer type: thyroid carcinoma



participant ID: 494fec2d-a438-4b21-903c-6ef07fb08fe4
cancer type: thyroid carcinoma



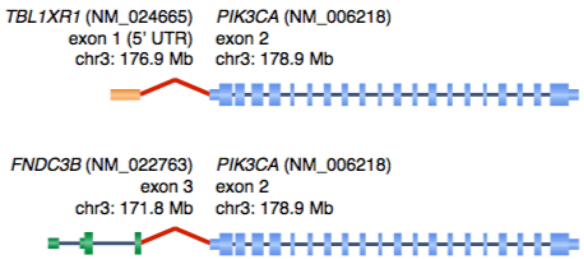
participant ID: 449ee008-36eb-4cb8-87f7-be76a568481f
cancer type: thyroid carcinoma

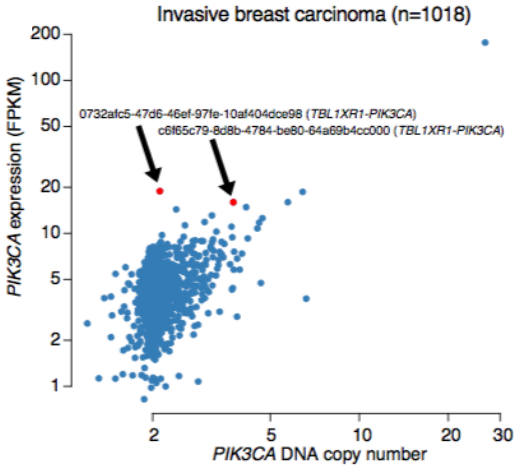


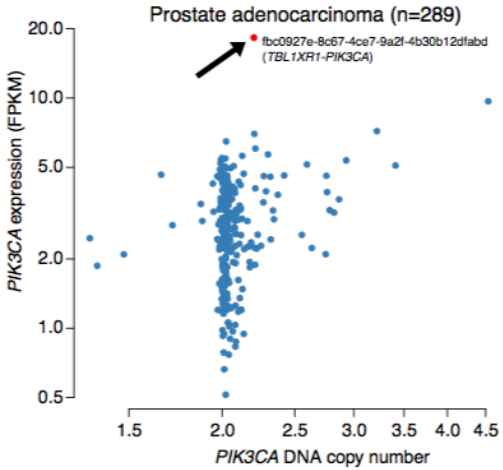
Novel Partners, all with dimerization motifs

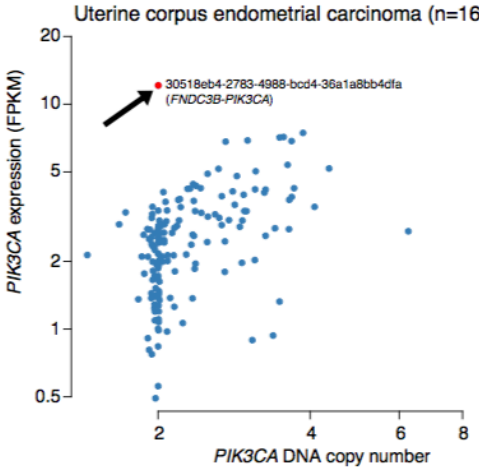
Novel *MET and PIK3CA* Fusions

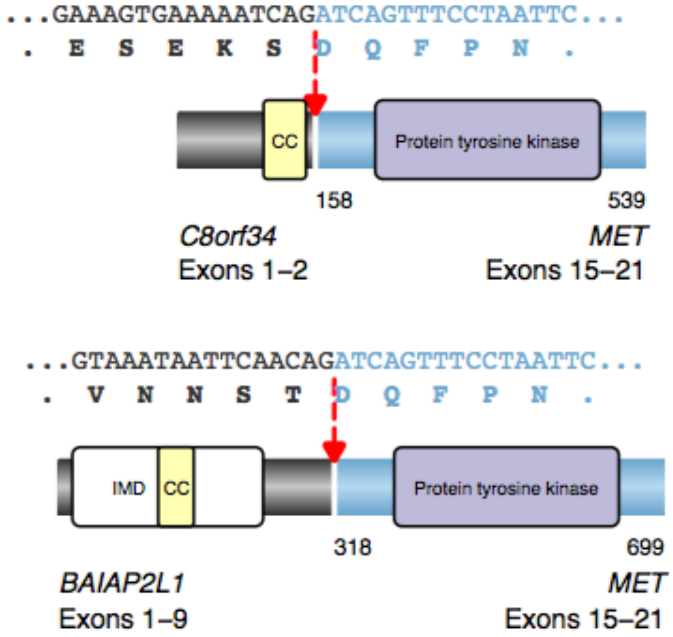
- *MET* and *PIK3CA* fusions occur in solid tumors where mutations and amplifications are already driver events





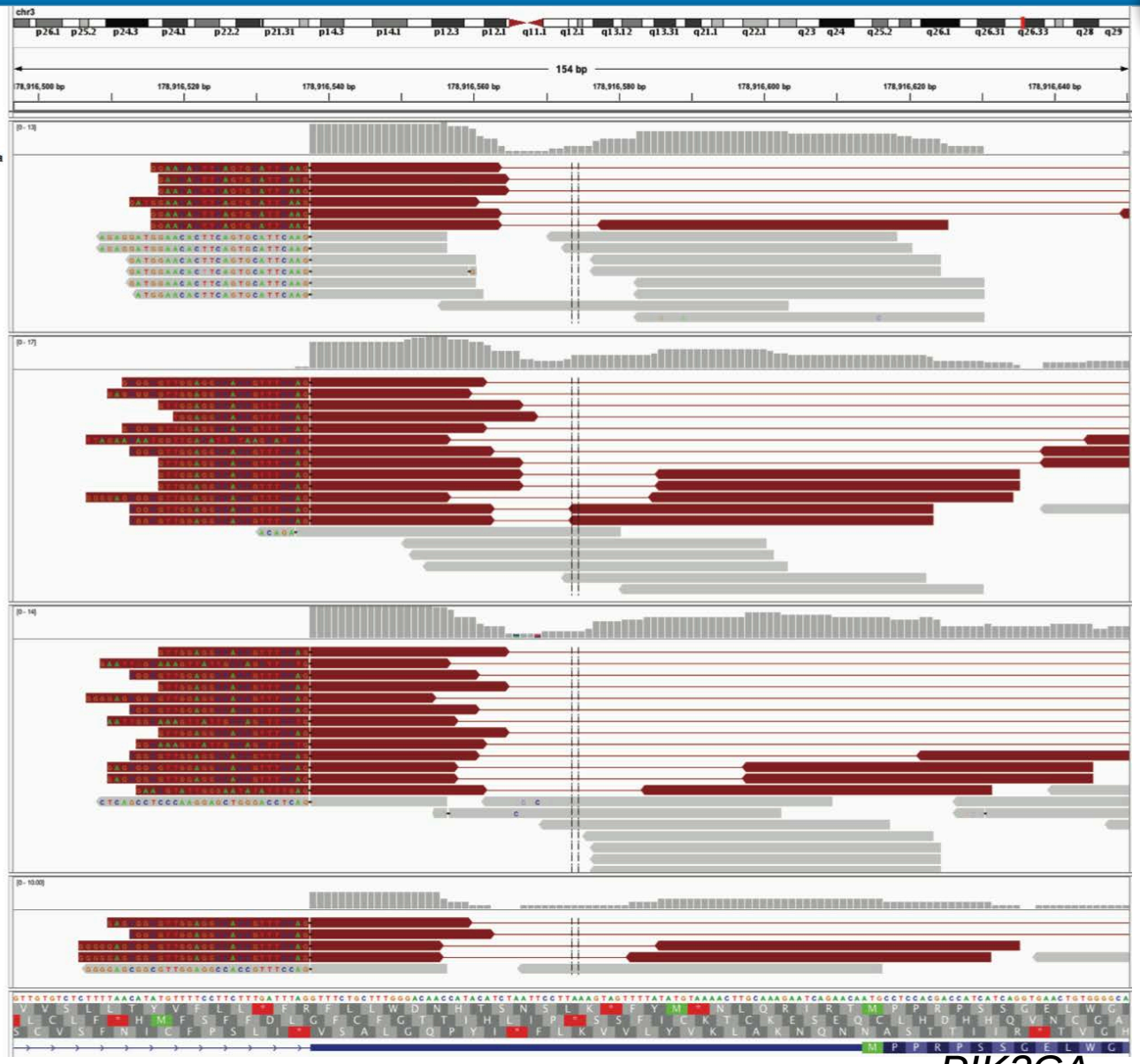






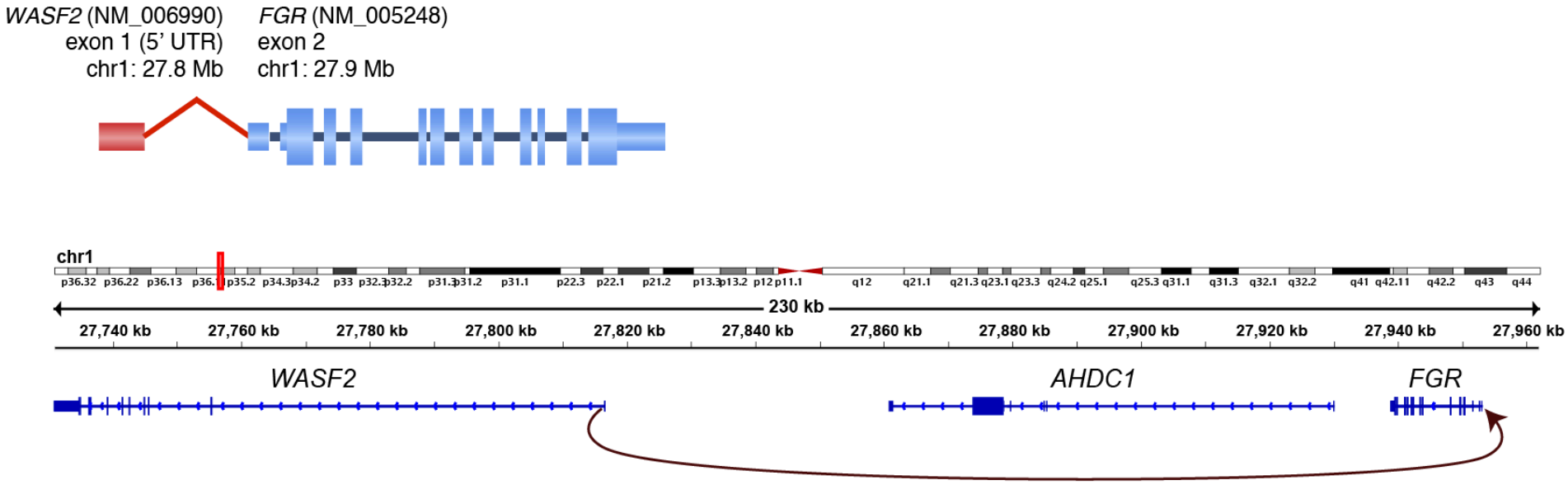
MET fusions in kidney papillary cell carcinoma

Novel *PIK3CA* fusions – supporting reads



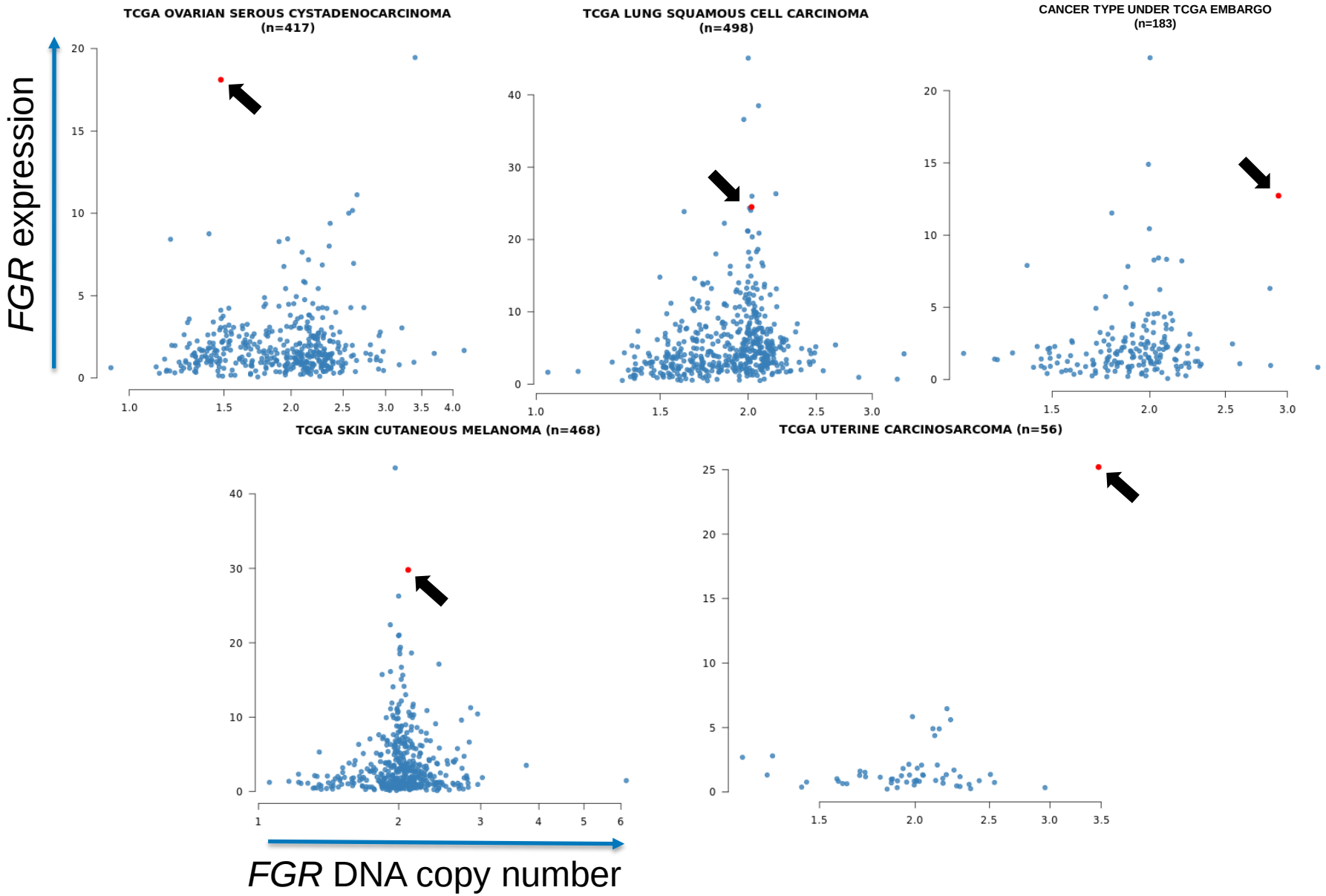
PIK3CA

New *WASF2-FGR* 5'-UTR Fusions



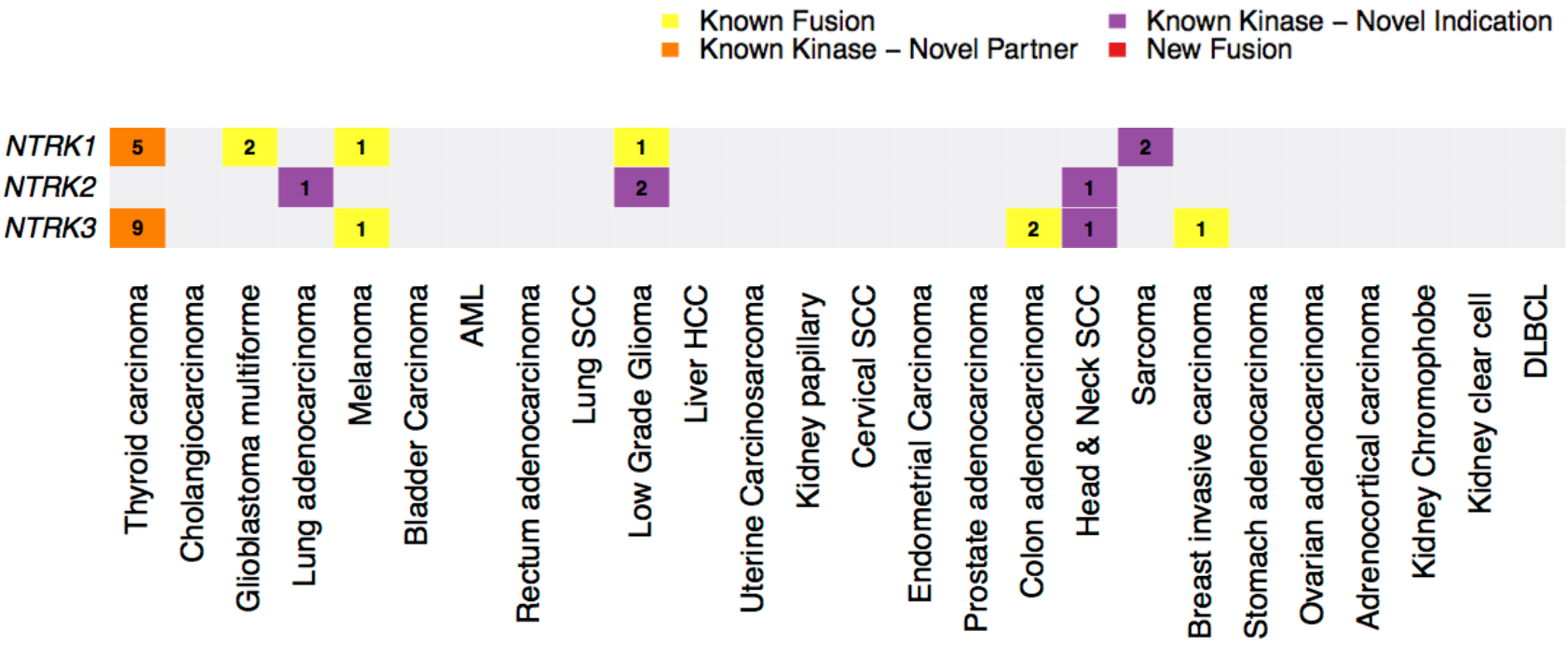
- Src family kinase
- Highly expressed in some hematopoietic cells and malignancies
- Oncogenic potential - viral oncogene homolog
- A new promoter fusion not previously implicated in cancer

New *WASF2-FGR* 5'-UTR Fusions



NTRK1/2/3 Fusions

- Certain fusions are very recurrent across tumors
  - 9/26 tumor types with *NTRK1/2/3* fusions for a total of 29 fusions
  - Additional recurrent fusions exist in other cancers under embargo



Summary

New insights into the kinase fusion "landscape"

- 6 additional TCGA cancer types surveyed
- 10% of *FGFR2* fusions in cholangiocarcinoma
- Novel *ALG14-JAK1* fusions
- 2 new *FGR* fusions in solid tumors
- New pan-cancer *NTRK1/2/*3 fusions
- PRKACA fusions in Liver cancer (FL-HCC)

Key Takeaways

- First pan-cancer fusion analysis
- New fusion analysis framework, designed with speed and sensitivity in mind
- Focus on kinase fusions as driver events
- Profound implications for diagnosis, patient treatment and drug discovery

Acknowledgements

- **The Cancer Genome Atlas**

- Blueprint Fusions team
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