Genome Medicine

RESEARCH HIGHLIGHT

# Novel cancer drivers: mining the kinome

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**Abstract**

Large-scale cancer genome studies are unveiling significant complexity and heterogeneity even in histopathologically indistinguishable cancers. Differentiating 'driver' mutations that are functionally relevant from 'passenger' mutations is a major challenge in cancer genomics. While recurrent mutations in a gene provides supporting evidence of 'driver' status, novel computational methods and model systems are greatly improving our ability to identify genes important in carcinogenesis. Reimand and Bader have recently shown that driver gene discovery in discrete gene classes (in this case the kinome) is possible across multiple cancer types and has the potential to yield new druggable targets and clinically relevant leads.

The overall goals of extensively characterizing cancer genomes are to refine current therapies through defining markers of therapeutic responsiveness or resistance, and to identify targets for the development of novel therapeutic strategies. Achieving these goals requires the integration of vast amounts of complex multidimensional genomic data with insights from other systems. A recently published study by Reimand and Bader provides a timely example of the importance of large-scale efforts in cancer genomics, and the valuable insights that mining these datasets can yield [1]. While cohort-based cataloguing of genomic aberrations initially reveals candidate driver events in different cancer types, this group and many others are also interrogating these data using innovative approaches to distinguish between driver and passenger mutations. In this study, cancer genome data from 800 patients across 8 cancer types made publicly available by the International Cancer Genome Consortium (ICGC) [2], the Cancer Genome Atlas (TCGA) [3,4] and independent groups [5] were analyzed using methods specifically designed to enrich for cancer drivers.

As we understand more about cancer genomes, profound complexity and heterogeneity are emerging [6]. Apart from mutations in a relative handful of cancer driver genes that occur in a significant proportion of tumors, the number of uncommon and rare mutations is extremely high. This poses challenges for the differentiation of drivers versus passengers, as most approaches focus on recurrently mutated genes, and less frequently mutated genes are probabilistically defined by comparison to the background mutation rate across the whole genome [7]. As a consequence, new approaches that increase confidence in candidate driver prediction are required to generate hypotheses for further study.

## Driver mutations in the cancer kinome

Reimand and Bader [1] focused their efforts on kinase genes that regulate phosphorylation, and regions of the genome that encode phosphorylation sites in known substrates, together known as the kinome. These classes of genes play important roles in growth, homeostasis and are often dysregulated in cancer. As such, they are attractive therapeutic targets and have in some instances resulted in the development of effective therapies (for example, Erlotinib® for the treatment of lung cancers that harbor *EGFR* mutations). The authors developed 'ActiveDriver', a novel computational algorithm that calculates the significance of non-synonymous single nucleotide variations within phosphoregulatory sites based on the local (gene-wide), rather than genome-wide background mutation rate, which assumes all areas of the genome have equal probability of harboring mutations. This approach increases the sensitivity of detection of significant events within a given region of the genome; in this case, the gene where the mutation of interest is located. ActiveDriver identified well-known cancer genes and showed that mutations at some specific phosphoregulatory sites within these were associated with differential patient survival. In addition, they identified novel candidate driver genes with existing functional data suggesting a role in carcinogenesis: *FLNB*, which has a role in cytoskeleton organization; *GRM1*, which increases

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**Table 1. Outline of strategies that can be used to enrich for, identify and refine candidate driver genes and mechanisms in cancer: the underlying rationale, experimental approaches and computational tools**

| Strategy | Rationale | Tools/data sources |
|---|---|---|
| Increasing sample size and clinical focus | Decrease variability due to different disease states | Statistical approaches; power calculations |
| Detect driver versus passenger events | Determine significance of recurrent mutations after controlling for background mutation rate, gene size and regional complexity | MutSig; MuSIC; GISTIC2.0 |
| Individual gene characteristics | Computationally predict functional consequences | ActiveDriver; CHASM; Polyphen2; SIFT; Mutationtaster |
| Integrative analysis and known characteristics of cancer drivers | Genomic characteristics of defined drivers inform functionally relevant events | Aligning genomic datasets (SNV, CNV, SV, methylation) |
| Pathway and network analysis | Heterogeneity of individual genetic aberrations contributing to common mechanisms | MsigDB; GeneGO; Reactome; PINA; PARADIGM |
| Integrative multidimensional data analysis | Orthogonal readouts of disease using different experimental approaches and model systems | GEMM; chemically induced models; mutagenesis screens; shRNA screens |
| Clinical correlation | Association with clinical characteristics may inform functional roles | Statistical methods |

CNV, copy number variation; GEMM, Genetically Modified Mouse Model; shRNA, short hairpin RNA; SNV, single nucleotide variation; SV, structural variation.

PI3K activity; and *POU2F1*, a POU domain transcription factor that regulates cell cycle progression. As a consequence, they conclude that ActiveDriver complements existing analysis tools.

Next, they performed network analysis and defined modules of kinases that were hierarchically organized, and found that certain networks were associated with differential survival in ovarian cancer. This has significant implications for therapeutic development, as defining key functional dependencies or 'weak points' in otherwise robustly deregulated mechanisms could uncover attractive therapeutic targets. They hypothesized that *PRKCZ* is one such master regulator of a frequently mutated phosphoregulatory network that contains well-known cancer genes such as *PTEN*, which is inactivated in many cancer types and functions as a tumor suppressor by negatively regulating Akt/PKB signaling. Although there are no drugs that directly target *PRKCZ*, multiple inhibitors of an immediately upstream kinase, *PDPK1*, are available.

## Strategies for enriching cancer driver genes

In general, several approaches can assist in enriching for candidate driver genes (Table 1) [8], many of which are exploited by Reimand and Bader [1]. These include the following approaches described below.

### Increasing sample size and/or focus on uniform clinically relevant groups to define low frequency recurrent events

Current activities in this area include pan-cancer analyses, which can examine single genes, networks and pathways. The ICGC/TCGA goal within the next few years is to generate comprehensive genomic data for in excess of 25,000 cancer genomes, and when combined with other efforts the number is projected to be even greater.

### Investigating the known characteristics of cancer genes

Reimand and Bader [1] exploited this in several ways: (1) choosing to focus on mutations in phosphoregulatory sites, (2) validating ActiveDriver by detecting well-known cancer genes, and (3) using insights from other studies. In addition, other characteristics such as recurrent inactivation of genes using different mechanisms (point mutation, deletion, methylation) in discovery efforts are supportive of a candidate tumor suppressor gene.

### Pathway and network analysis

Numerous pathway analysis tools are available (for example, MsigDB, GeneGO and Reactome), and as the underlying information grows, hypotheses concerning function and mechanisms can be better developed.

### Integrative analysis

Orthogonal global analysis using different methodologies can assist in enriching for candidate driver genes and pathways. These datasets can include other genomic analyses; for example, transcriptome, epigenome or incorporate model systems such as animal models (comparative genomics), or *in vitro* functional screens [9].

### Identifying clinical correlates

Correlating with clinical parameters such as prognosis and therapeutic responsiveness can be supportive of functional relevance of a mutated gene or pathway/network. Further insights can be gained if there is association with distinct clinical features such as the pattern of disease spread, vascular invasion, lymph node

metastasis and perineural invasion. Reimand and Bader identify associations with survival for both specific single gene events and networks [1].

## Summary

Reimand and Bader [1] used large datasets for the purpose they were created; they developed a novel approach to address current challenges in analyzing genomes and used multiple methods to provide significant insights into the molecular pathology of cancer. These data provide increased confidence in pursuing these target mechanisms through more detailed experimentation. We are only at the beginning of mapping out the genomic events that exist in cancer, and the data analyzed in this report examined somatic single nucleotide variants in the protein coding regions of genes [10]. Other classes of pathogenic mutation such as insertions, deletions, and translocations can dramatically impact gene function and also warrant investigation. Furthermore, other levels of gene regulation such as epigenetic modification and RNA-mediated events can be integrated into these studies over time. As the cancer genome atlases continue to grow, it is anticipated the approach described in the Reimand and Bader study will lead to further significant insights into the underlying mechanisms that play key roles in cancer. This is vitally important for more timely advances in intervention strategies for cancer prevention, early detection and treatment.

### Abbreviations

ICGC, International Cancer Genome Consortium; TCGA, The Cancer Genome Atlas.

### Competing interests

The authors declare that they have no competing interests.

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### References

1. Reimand J, Bader GD: **Systematic analysis of somatic mutations inphosphorylation signaling predicts novel cancer drivers.** *Mol Syst Biol* 2013, **9:**637.
2. International Cancer Genome Consortium, Hudson TJ, Anderson W, Artez A, Barker AD, Bell C, Bernabe RR, Bhan MK, Calvo F, Eerola I, Gerhard DS, Guttmacher A, Guyer M, Hemsley FM, Jennings JL, Kerr D, Klatt P, Kolar P, Kusada J, Lane DP, Laplace F, Youyong L, Nettekoven G, Ozenberger B, Peterson J, Rao TS, Remacle J, Schafer AJ, Shibata T, Stratton MR, Vockley JG, Watanabe K, Yang H, Yuen MM, Knoppers BM, Bobrow M, Cambon-Thomsen A, Dressler LG, Dyke SO, Joly Y, Kato K, Kennedy KL, *et al.*: **International network of cancer genome projects.** *Nature* 2010, **464:**993-998.
3. Cancer Genome Atlas Research Network: **Comprehensive genomic characterization defines human glioblastoma genes and core pathways.** *Nature* 2008, **455:**1061-1068.
4. Cancer Genome Atlas Research Network: **Integrated genomic analyses of ovarian carcinoma.** *Nature* 2011, **474:**609-615.
5. Jones S, Zhang X, Parsons DW, Lin JC, Leary RJ, Angenendt P, Mankoo P, Carter H, Kamiyama H, Jimeno A, Hong SM, Fu B, Lin MT, Calhoun ES, Kamiyama M, Walter K, Nikolskaya T, Nikolsky Y, Hartigan J, Smith DR, Hidalgo M, Leach SD, Klein AP, Jaffee EM, Goggins M, Maitra A, Iacobuzio-Donahue C, Eshleman JR, Kern SE, Hruban RH, *et al*: **Core signaling pathways in human pancreatic cancers revealed by global genomic analyses.** *Science* 2008, **321:**1801-1806.
6. Samuel N, Hudson TJ: **The molecular and cellular heterogeneity of pancreatic ductal adenocarcinoma.** *Nat Rev Gastroenterol Hepatol* 2011, **9:**77-87.
7. Dees ND, Zhang Q, Kandoth C, Wendl MC, Schierding W, Koboldt DC, Mooney TB, Callaway MB, Dooling D, Mardis ER, Wilson RK, Ding L: **MuSiC: Identifying mutational significance in cancer genomes.** *Genome Res* 2012, **22:**1589-1598.
8. Eifert C, Powers RS: **From cancer genomes to oncogenic drivers, tumour dependencies and therapeutic targets.** *Nat Rev Cancer* 2012, **12:**572-578.
9. Biankin AV, Waddell N, Kassahn KS, Gingras MC, Muthuswamy LB, Johns AL, Miller DK, Wilson PJ, Patch AM, Wu J, Chang DK, Cowley MJ, Gardiner BB, Song S, Harliwong I, Idrisoglu S, Nourse C, Nourbakhsh E, Manning S, Wani S, Gongora M, Pajic M, Scarlett CJ, Gill AJ, Pinho AV, Rooman I, Anderson M, Holmes O, Leonard C, Taylor D, *et al.*: **Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes.** *Nature* 2012, **491:**399-405.
10. Green ED, Guyer MS: **Charting a course for genomic medicine from base pairs to bedside.** *Nature* 2011, **470:**204-213.

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