An Algorithm for Identifying Druggable Targets Among Influential Mutations in Individual Cancer Patients

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INTRODUCTION

- Genomic alterations such as mutations and copy number variations are causative factors of cancer. A few of these will have a significant impact in modulating multiple pathways and are termed 'driver mutations', while a majority are typically thought of as less influential and are termed 'passenger mutations'.
- Influential mutations that harbour alterations in their small molecule binding sites are attractive drug target candidates as they can be used to selectively target the tumor.
- The landscape of these mutations varies enormously across patients, especially in cancers with high heterogeneity.
- Computational methods are available for identifying driver mutations by analysing whole genome sequences from tumours. Most of these however depend on the frequency of occurrence of a mutation.
- In heterogeneous cancers (e.g. liver cancer), the number of frequently occurring mutations is negligible.

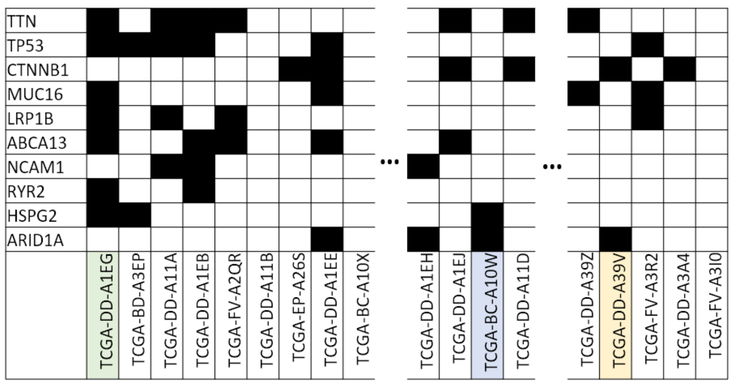
OBJECTIVE

- Identify influential and druggable mutations, given data for only 1 patient.

CHALLENGES

- Among the 48 matched tumor-normal samples in TCGA-LIHC (liver cancer), the most common mutation occurs in only 17 patients.

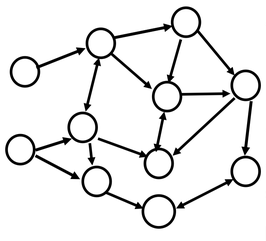
TCGA-LIHC – 10 most frequent mutations



RATIONALE

- A mutated gene is *influential* if
  - it belongs to the most perturbed zone in the cancer condition – captured by extracting the top response network
  - it has a central position in the perturbed processes – captured by computing centrality in the top response network
  - it has an impact on a large number of differentially expressed genes through known protein-protein or regulatory interactions – captured by ranking based on reachability of DEGs through highly active paths

Input 1. Protein-protein interaction network



Human interaction network*

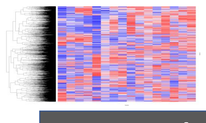
· Sources: In-house curated network (STRING v 10, SignaLink v 2.0, Cancer Cell Map, BioGRID, Multinet)

· Genes (nodes): 17,062

· Interactions (edges): 2,08,760

*Network published in NPJ Systems Biology

Input 2. Gene expression data



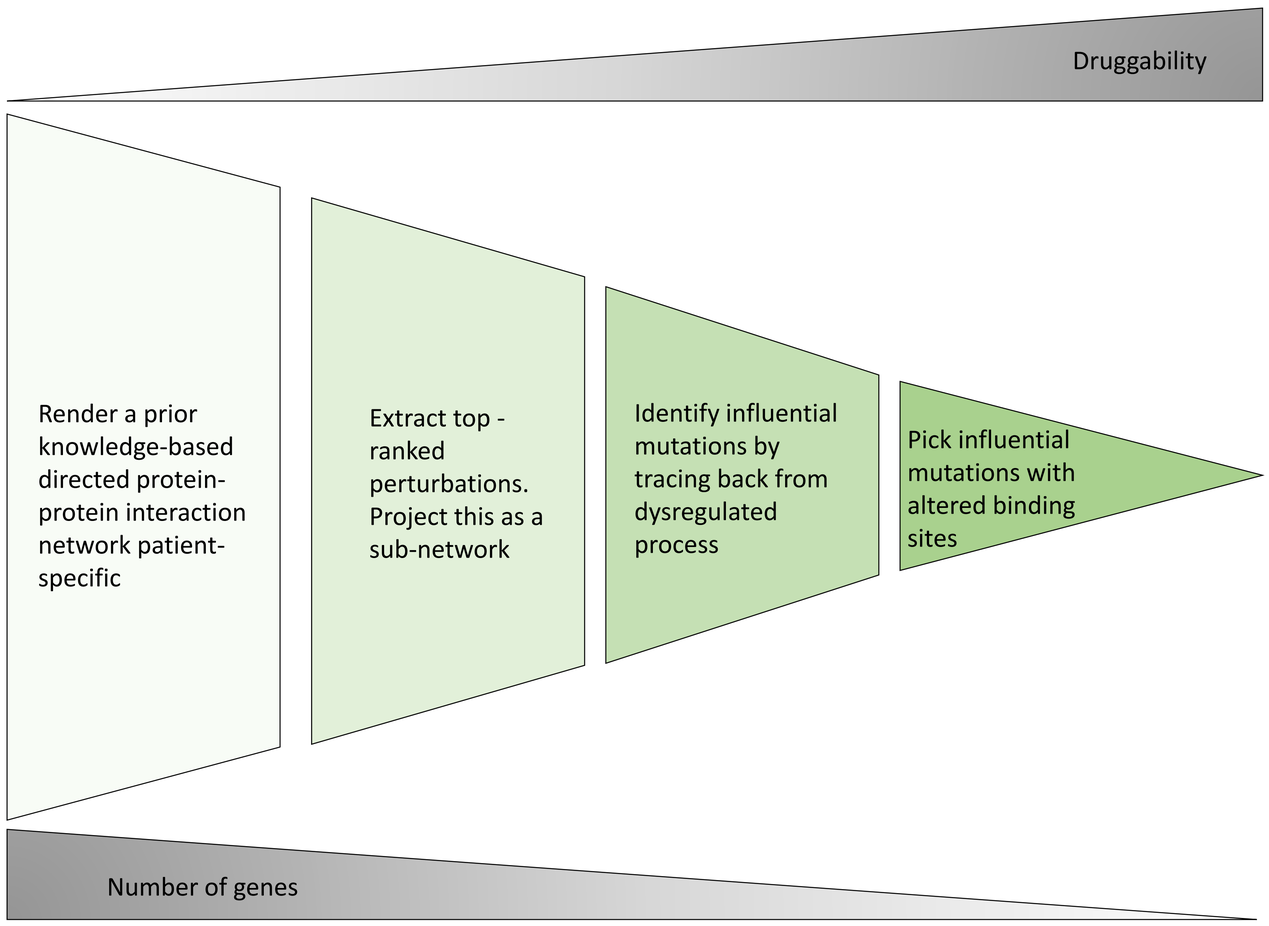
TCGA-LIHC liver cancer dataset

- 48 matched tumor and normal samples extracted

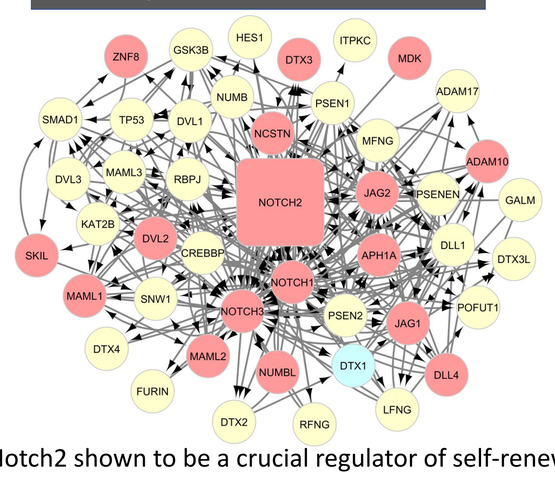
Input 3. Mutation data

List of mutated genes, along with the actual mutation itself.

METHOD - IMut



Example influential mutation



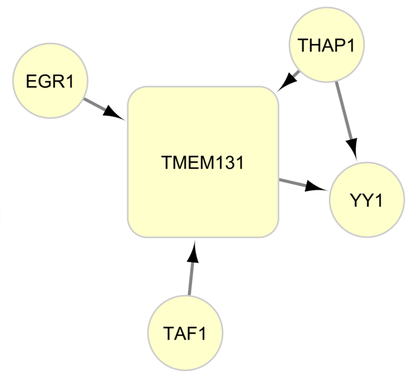
Up-regulated gene

Down-regulated gene

Gene with unchanged expression

Mutated gene

Example non-influential mutation



Notch2 shown to be a crucial regulator of self-renewal and tumorigenicity in human hepatocellular carcinoma cells [2].

TMEM131 is associated with TMEM131 include Subdural Empyema and Streptococcal Meningitis [1].

RESULTS – Case study patient 1, TCGA-DD-A39V

- **54 mutated** genes
- **9 influential** mutations
- **p-value < 0.01** for hypergeometric test calculated w.r.t mutations known to be causally linked to cancer as per **CGC** [3].

Predicted investigational drug targets

- **CTNNB1 – Catenin Beta 1**
- The protein encoded by this gene is part of a complex of proteins that constitute adherens junctions (AJs). The encoded protein also anchors the actin cytoskeleton and may be responsible for transmitting the contact inhibition signal that causes cells to stop dividing once the epithelial sheet is complete [1].
- Under investigation as combination therapy for hepatocellular carcinoma patients (**clinicaltrials.gov identifier NCT03212625**).

- **NFE2L2 - Nuclear Factor, Erythroid 2 Like 2**
- Encodes a transcription factor which acts as a basic leucine zipper (bZIP). Known to regulate genes related to antioxidant response elements (ARE) [1].
- Sulforaphane, which targets NFE2L2, is being tested in clinical trials for the treatment of lung and prostate cancer [4] (**clinicaltrials.gov identifiers NCT03232138 and NCT01228084**).

- **DHCR24 - 24-Dehydrocholesterol Reductase**
- Encodes a flavin adenine dinucleotide (FAD)-dependent oxidoreductase. Protects cells from oxidative stress during apoptosis induced by oxidative stress. Also protects against amyloid-beta peptide-induced apoptosis [1].
- Being investigated as a target in several cancers [5].

References

[1] Safran, Marilyn, et al. "GeneCards Version 3: the human gene integrator." Database 2010 (2010).

[2] Wu, Wen-Rui, et al. "Notch2 is a crucial regulator of self-renewal and tumorigenicity in human hepatocellular carcinoma cells." Oncology reports36.1 (2016): 181-188.

[3] Futreal, P. Andrew, et al. "A census of human cancer genes." Nature Reviews Cancer 4.3 (2004): 177.

[4] Tong, Ying-Hui, et al. "Keap1–Nrf2 pathway: A promising target towards lung cancer prevention and therapeutics." Chronic diseases and translational medicine 1.3 (2015): 175-186.

[5] Müller, Christoph, et al. "New chemotype of selective and potent inhibitors of human delta 24-dehydrocholesterol reductase." European journal of medicinal chemistry 140 (2017): 305-320.