# An integrative ENCODE resource for cancer: interpreting non-coding mutations and gene regulation

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## Abstract

ENCODE comprises thousands of functional genomics data sets, related to numerous cancer types; it is possible to tailor them into a targeted resource for interpreting cancer genomes. In particular, this resource can be used to measure the impact of non-coding mutations, which constitute the overwhelming majority of somatic variants. By integrating novel assays (e.g. STARR-seq) with many epigenetic features, we can significantly refine and compactify annotations (beyond a more generic genome annotation), increasing the power for recurrent-mutation detection. Besides, ENCODE functional characterization signal data, especially replication timing, allows us to build precise, cancer-matched background models for mutation rates considerably more accurate than previous models. In addition, ENCODE data allows the construction of various regulatory networks, incorporating new assays, such as Hi-C and RNA-binding protein assays (i.e., eCLIP), in addition to large-scale TF ChIP-seq. In some contexts, these networks reveal how connections are rewired during oncogenesis, as well as how such transformation relates to the STEM-like state. More generally, these ENCODE networks can be used to prioritize regulators most associated with large-scale expression changes in cancer. Combining the networks with the refined annotations and background models, we develop a step-wise prioritization scheme for non-coding mutations. Here, we demonstrate how this can be instantiated in practice, and we perform a number of small-scale validations (ie luciferase assays and shRNA RNA-seq) to demonstrate how the resource can reliably prioritize mutations with significant consequences in cancer.

## Introduction

Large-scale functional genomics data are useful for dissecting cancer genomes, particularly for interpreting mutation and expression profiles. Lines of integrative studies were performed based on the initial ENCODE release in 2012 and other targeted functional genomic data. In particular, such data allows us to assign functional impact to non-coding mutations, which form the overall bulk of mutations in the cancer genome. For instance, Torchia *et al*. integrated various genomic and epigenetic signals to identify promising therapeutic targets in rhabdoid tumors. Secondly, the ENCODE data, particularly, the replication time data and other signal data is useful for estimating background mutation rates (BMR), which vary greatly over the genome. Lawrence et al. incorporated genome-wide features, such as replication timing, methylation, and expression profiles, to identify cancer drivers after BMR correction. ENCODE data is also useful for connecting non-coding elements (such as enhancers or promoters) into regulatory networks, which are pivotal for understanding cancer from a systems-biology perspective. For example, Leiserson *et al* discovered significantly mutated subnetworks that contain well-known cancer signaling pathways in various cancer types.

The new release of ENCODE data has a number of improvements over the last release, which allows us to construct EN-CODEC (a customized “companion ENCODE encyclopedia resource for Cancer”) by integrating 2656 experiments from 14 experimental assays in 229 cell types. It comprises three parts: a background mutation rate model, compact annotations, and regulatory networks. We detail each below and provide illustrations of how they may be used to dissect cancer genomes after combining mutation and expression profiles from large cancer cohorts such as TCGA.

Specifically, with a much wider selection of ENCODE cell types, the resource provides substantially more functional genomics data that can be better matched to particular cancer types of interest, allowing a demonstrably improved BMR model. In addition, for a number of well-known cancer cell types, it incorporates novel various assays (such as STARR-Seq, HiC, and ChIA-pet) together with a large battery of histone markers to accurately define core enhancers and their targets. Consequently, EN-CODEC constructs more compact annotations than generic ones to maximize statistical power in search of mutationally burdened regions. Finally, the resource significantly extends TF regulatory networks and constructs additional networks from novel assays such as eCLIP and HiC. In a few prominent cancer types, these provides cell type-specific networks in both tumor and normal cells, which enables us to directly measure regulatory changes during the normal-to-tumor transition. Furthermore, the stem cell data in ENCODE further relates such rewiring events as toward or away from stem-like state. More generally, our EN-CODEC network can better explain cancer-specific expression patterns derived from cancer patients from resources as TCGA, and help pinpoint key regulators that drive large-scale tumor-to-normal expression changes.

We combined the network analysis with the compact annotation and mutational burdening (from the enhanced background model) to propose a step-wise prioritizing scheme. We validated the functional impact of prioritized mutations and elements using small-scale experiments such as shRNA-seq and luciferase assays. We emphasize this as an illustration of how new annotation sets can immediately be used to analyze existing cancer mutation data and cancer expression.

## Multi-level data integration improves variant recurrence analysis in cancer

One of the most powerful ways of identifying key elements in cancer genomes is through mutation recurrence analysis, the objective of which is to discover regions having more mutations than expected. Hence, we demonstrate how to integrate extensive ENCODE data to construct an accurate background mutation rate model in a wide range of cancer types. BMR estimation is challenging: the somatic mutation process can be influenced by numerous confounders (in the form of both external genomic factors and local sequence context factors), and these can result in wrong conclusions if not appropriately corrected10.

We address the issues associated with confounding factors in a cancer-specific manner. Specifically, we separated the whole-genome into bins (1Mb) and calculated mutation counts per bin under each local context category. For each category for a BMR prediction, we used a negative binomial regression of the mutation counts against 475 genomic features across 229 cell types, including replication timing, chromatin accessibility, Hi-C, and expression profiles. In contrast to methods that use data from unmatched cell types10 , our approach automatically selects the most relevant features, thereby providing noticeable improvements in BMR estimation (Fig 2A). For example, matched replication timing data in general significantly outperforms data from unmatched HeLa-S3 cell line. Notably, the combination of many different genomic features significantly improves the estimation accuracy in multiple cancer types (Fig 2 B). Consistent with previous results on mutation rates, in breast cancer, we observed an elevated rate in regions with the repressive modification H3K9me3 and a reduced rate in regions with the activating, enhancer-associated mark H3K27ac11-13. Also, due to the correlated nature of genomic features across cell types, even approximate matching of a specific cancer against an ENCODE cell line can still improve its BMR estimation. Hence, our analyses may easily be extended to other cancer types.

 A second aspect to best using the ENCODE data in cancer mutation analysis is maximizing the statistical power of burden tests. In traditional genomic analyses, a comprehensive set of annotations, usually covering as many base pairs as possible, is considered to be beneficial. However, testing every possible nucleotide in the genome in mutation recurrence analysis noticeably reduces statistical power. Here we aim to increase the power of burden test by multi-level data integration from several aspects. First, for a single burden test on an individual genomic element (e.g., an enhancer), focusing on a smaller, "core" region, enriched for true functional impact, would significantly improve detectability (see supplement). Hence, we trimmed the conventional annotations to key "functional territories" by using the TF-binding sites (TFBS) and the shapes of various genomic signals (see supplement). Second, repeated burden tests on a large number of elements, would be subject to large penalty from multiple-testing correction. We, therefore, tried to develop a minimum number of high-confidence annotations in our search for burdened regions by removing low-confidence ones as much as possible. With a particular focus on enhancers, we started by searching for regions supported by multiple lines of evidence in the data-rich top-tier cell types. We developed a machine-learning algorithm to combine shapes of signal tracks from DNase-seq and a battery of up to 10 histone modification marks. We then intersected these predictions with those of putative enhancers called from STARR-seq experiments (using a second algorithm). These experiments provide a direct, albeit noisy, readout of enhancer activity in particular cell types. Such an integrative approach enables us to define a minimal list of enhancers with as few false-positives as possible (see supplement). We also reconciled and cross-referenced our "compact annotation" with the main encyclopedia annotations (see supplement).

A final aspect of our compact annotation to increase statistical power is linking the noncoding regulatory elements to protein-coding exons to form an extended gene region as a single test unit. Such a unified annotation enables joint evaluation of the mutational signals from distributed yet biologically connected genomic regions. Traditional methods for linking rely solely on the correlation of individual signals (e.g., between the activity of one histone mark at enhancer and gene expression of neighboring genes) and potentially result in inaccurate extended gene definitions. Here, we use direct experimental evidence and physical interactions from Hi-C and ChIA-PET experiments, combined with a machine learning algorithm that takes into consideration the wide variety of histone modification marks and gene expression to achieve accurate enhancer-target gene linkages.

Putting together our compact annotation, BMR estimation, and accurate extended gene definitions allows us to get maximal power in detecting genomic regions, coding and non-coding, burdened by mutations (Fig 2C). For example, in the context of chronic lymphocytic leukemia (CLL), our analysis identified well-known highly mutated genes, such as TP53 and ATM that have been reported from previous analyses. It also discovered genes missed by the exclusive analysis of coding regions, such as BCL6. This gene has strong prognostic value for patient survival (Fig. 2D).

## Using ENCODE regulatory networks to interpret tumor expression profiles and identify key regulators in cancer

EN-CODEC provides detailed regulatory networks directly based on experimental assays suitable for cancer research. Specifically, for TF networks, we incorporated both distal and proximal networks by linking TFs to genes, either directly by TF-promoter binding or indirectly via TF-enhancer-gene interactions in each cell type. We then pruned these networks to include only the strongest edges using a signal shape algorithm14. In addition, we reconciles all our cell-type-specific networks to form a generalized pan-cancer network. Similarly, we also defined an RNA-binding protein (RBP) network. Compared to imputed networks from gene expression or motif analysis, our ENCODE TF and RBP networks were built using actual ChIP-seq and eCLIP experiments, which provide much more accurate regulatory linkages between functional elements.

These networks are useful for interpreting the gene expression data from tumor samples. In particular, using a machine learning method, we integrated 8,202 tumor expression profiles from TCGA to systematically search for the TFs and RBPs most strongly driving tumor-specific expression. For each patient, we tests the degree to which regulators’ activity correlates with their targets' tumor-to-normal expression changes. We then calculated the percentage of patients with these relationships in each cancer type and presented the overall trends for key TFs and RBPs in Fig. 3A.

As expected we found that the target genes of MYC are significantly up-regulated in numerous cancers, which is consistent with its well-known role as an oncogenic TF15. We further validated MYC’s regulatory effect through knockdown experiments (Fig 3). Consistent with our predictions, the expression of MYC targets is significantly reduced after MYC knockdown (Fig 3B). We then used the regulatory network to understand how MYC works with other TFs. We first looked at all triplets involving MYC, requiring that a second TF both interacts with and shares a common target with MYC. In all cancer types, we found that MYC’s expression levels are positively correlated with the expression levels of most of its targets, while the second TF shows only limited influence as determined by partial correlation analysis.

We further investigated the exact structure of these regulatory triplets. The most common one is the well-understood feed-forward loop (FFL). In this case, MYC regulates both another TF and a common target of both MYC and that TF (Figure 3 C). Since MYC amplification is a major determinant of many cancers, understanding which TFs appear to further amplify its effects may yield insights for efforts aimed at MYC inhibition16. Most of these FFLs we observed involve well-known MYC partners such as MAX and MXL1. However, we also discovered many involve NRF1. Upon further examination, we found that that the MYC-NRF1 FFL relationships were mostly coherent, i.e., "amplifying" in nature. We further studied these FFLs by organizing them into logic gates, in which the two TFs act as inputs and the target gene expression represents the output17. We show that most of these gates follow either an OR or MYC-always-dominant logic gate. Thus, the ENCODE regulatory network not only identifies key cancer regulators, but also demonstrates how they work in combination with other regulators.

We also analyzed the ENCODEC RBP-network and found key regulators associated with cancer. For example, the ENCODE eCLIP profile for the RBP SUB1 has peaks enriched on the 3’UTR regions of genes, and the predicted targets of SUB1 were significantly up-regulated in many cancer types (Fig. 3C). As an RBP, SUB1 has not previously been associated with cancer, so we sought to validate its role. Knocking down of SUB1 in HepG2 cells significantly down-regulated its targets (Fig. 3D), and the decay rate of SUB1 targets is significantly lower than non-targets (see supplement). Moreover, we found that the up-regulation of SUB1 targets is correlated with a poorer patient survival in some cancer types, such as lung cancer (Fig. 3D). These results suggest that SUB1 may have an oncogenic role.

We further analyzed the overall TF regulatory network by systematically arranging it into a hierarchy (Fig 4). Here, TFs are placed on different levels such that those in the middle tend to regulate TFs at the bottom and, in turn, are more regulated by top-level18. In the hierarchy, we found that the top-layer TFs not only enriched in cancer associated-genes but also more significantly drive differential gene expressions in tumors.

## Measuring extensive rewiring events in cell-type specific TF regulatory networks

For the top-tier cell types with numerous TF ChIP-seq experiments, our EN-CODEC resource contains cell-type-specific regulatory networks for several cancer types, which enables direct comparison with networks built from their paired normal cell types. We proposed the concept of a “composite normal” by reconciling multiple related normal cell types (see supplement). The pairings -- relating cancerous cell lines to specific tumors and then matching them to normal cell types -- are approximate in nature. However, many of these pairings have been widely used in the literature before (see supplement). Furthermore, they leverage the extensive functional characterization assays in ENCODE to provide us with a novel opportunity to directly understand the regulatory alterations in cancer.

In particular, in "tumor-normal pairs", we measured the signed, fractional number of edges changing -- what we call the “rewiring index" -- to study how the targets of each common TF changed over the course of oncogenic transformation. In Fig. 5A, we ranked TFs according to this index. In leukemia, well-known oncogenes (such as MYC and NRF1) were among the top edge gainers, while the well-known tumor suppressor IKZF1 is the most significant edge loser (Fig 5A). Mutations in IKZF1 serve as a hallmark of various forms of high-risk leukemia19-21. We observed a similar trend in TFs using distal, proximal, and combined network (see details in supplement). The trend was consistent across cancers: highly rewired TFs such as BHLHE40, JUND, and MYC behaved similarly in lung, liver, and breast cancers (Fig 5).

In addition to direct TF-to-gene connections, we also measured rewiring using a more complex gene community model. The targets within the TF regulatory network were characterized by heterogeneous network modules (so called "gene communities"), which come from multiple biologically relevant genes. Instead of directly measuring the changes in a TF's targets between tumor and normal, we determined the changes in its gene communities via a mixed-membership model. Similar patterns to the direct rewiring were observed using this model (Fig 5A).

We next tested whether the gain or loss events from the normal-to-tumor transition result in a network that is more or less similar to that in stem cells like H1-hESC. Interestingly, the gainer TF group tends to rewire away from the stem cell’s regulatory network, while the loser group is more likely to rewire toward the stem cell.

The majority of rewiring events were associated with noticeable gene expression and chromatin status changes, but not necessarily with mutation-induced motif loss or gain events (Fig. 5A). This is consistent with previous discoveries that most non-coding risk variants are not well-explained by the current model22. For example, JUND is a top gainer in K562. The majority of its gained targets in the tumor demonstrate higher gene expression, stronger active and weaker repressive histone modification mark signals, yet few of its binding sites are mutated. We found a similar trend for the rewiring events associated with JUND in liver cancer and, largely, for other factors in a variety of cancers, with some notable exceptions (see supplement). Related to this, we organized the cell-type-specific networks into cell-type-specific hierarchies, as shown in Figure 4. Specifically, in blood cancer, the more mutationally burdened TFs sit at the bottom of the hierarchy, whereas the TFs more associated with driving cancer gene expression changes tend to be at the top.

## Step-wise prioritization schemes pinpoint deleterious SNVs in cancer

Summarizing the analysis above, the EN-CODEC resource consists of annotations summarized in Fig. 6 : (1) a BMR model with matching procedure for relevant functional genomics data and a list of regions with higher-than-expected mutational burden in a diverse selection of different cancers; (2) highly accurate, minimal and compactly defined enhancers and promotors found from integrating many functional assays, including STARR-seq; (3) enhancer-target-gene linkages and extended gene neighborhoods, obtained by integrating linkages from Hi-C and multi-histone mark and expression correlation; (4) tumor-normal differential expression, chromatin, and regulatory changes; (5) TF regulatory networks, both merged and cell-type specific, based on both distal and proximal regulation; (6) for each TF, its position in the network hierarchy and rewiring status; and (7) an analogous but less-developed network for RBPs.

Collectively, these resources allow us to prioritize key features as being associated with oncogenesis. Our prioritization scheme is shown in as a workflow in Fig. 6A. We first search for key regulators that are frequently rewired, located at the network hubs, sit at the top of the network hierarchy, or significantly drive expression changes in cancer. We then prioritize functional elements that are associated with these regulators, are highly mutated in tumors, or undergo large changes in gene expression, TF binding, or chromatin status. Finally, on a nucleotide level, we pinpoint impactful SNVs for small-scale functional characterization by their ability to disrupt or introduce specific binding sites, or which otherwise occur in positions under strong purifying selection.

Using this framework, we subjected some key regulators, such as MYC and SUB1, to knockdown experiments in order to validate their regulatory effects in particular cancer contexts (Fig 3D). We also identified several candidate enhancers in noncoding regions associated with breast cancer, and validated their ability to influence transcription using luciferase assays in MCF-7. We selected key SNVs, based on mutation recurrence in breast-cancer cohorts within these enhancers that are important for controlling gene expression. Of the eight motif-disrupting SNVs that we tested, six exhibited consistent up- or down-regulation relative to the wild type in multiple biological replicates. One particularly interesting example, illustrating the unique value of ENCODE data integration, is in an intronic region of CDH26 in chromosome 20 (Fig. 6C). The shape of both histone modification and chromatin accessibility (DNase-seq) signals indicate its active regulatory role as an enhancer in MCF-7. This was further confirmed by STARR-seq (Fig. 5D). Hi-C and ChIA-PET data indicated that the region is within a topologically associated domain and validated a regulatory linkage to the downstream breast-cancer-associated gene SYCP223,24. We observed strong binding of many TFs in this region in MCF-7. Our motif-based analysis predicts that the particular mutation from a breast cancer patient significantly disrupts the binding affinity of several TFs, such as FOSL2, in this region (Fig. 6D). Luciferase assays demonstrated that this mutation introduces a 3.6-fold reduction in expression relative to the wild-type, indicating a strong repressive effect on this enhancer's functionality.

## Conclusion

This study highlights the value of our EN-CODEC companion to the main ENCODE encyclopedia as a resource for cancer research. By integrating 2656 experiments from 14 different types of assays, we first demonstrate that we can construct an accurate BMR model for a wide range of cancers and customize non-coding annotations to maximize their power in mutational burdening calculations. We also built extensive regulatory networks from thousands of ChIP-seq and eCLIP experiments to directly study the regulatory changes associated with cancer, as well as highlight key regulators. Finally, we leveraged the resource to provide a prioritization scheme to pinpoint key elements for follow-up experiments.

[JZ2ALL: I like the following para but it is too repeatative to the introduction part]

EN-CODEC comprises three resources: 1) compact annotations that is suitable for reccurent-mutation dectection by maximizing statistical power; 2) cancer-specific BMR models with significantly increased accuracy; 3) various regulatory networks and hierarchies for both pan-cancer and cancer-specific studies. For several data-enriched cancer types, it provides cancer-specific resources from pairing the top-tier cell lines to particular cancer types. We realize that the representative tumor and normal cell types and their pairings used here are rough in nature. However, cancer is a heterogeneous disease such that even the tumor cells from one patient usually show distinct molecular, morphological, and genetic profiles2. It is difficult to obtain a "perfect" match even from real tumor and normal tissues taken from a single patient.

Our study underscores the value of large-scale data integration, and we note that expanding the scale of our approach is straightforward. For example, a larger number of genomic features from matched cell types could result in better BMR estimation; more advanced functional characterization assays may generate further compact annotation sets, and more ChIP-seq/eCLIP experiments on additional factors would provide more detailed regulatory networks. Larger patient cohorts of expression and mutation profiles from many cancer types may be used to discover novel key features in cancer genomes. We also anticipate that an additional step may entail carrying out many assays on specific tissues and tumor samples. We hope that we demonstrate here that such large-scale integration is technically feasible and provides further opportunities for the future.

## Reference

1 Weinhold, N., Jacobsen, A., Schultz, N., Sander, C. & Lee, W. Genome-wide analysis of noncoding regulatory mutations in cancer. *Nat Genet* **46**, 1160-1165, doi:10.1038/ng.3101 (2014).

2 Meacham, C. E. & Morrison, S. J. Tumour heterogeneity and cancer cell plasticity. *Nature* **501**, 328-337, doi:10.1038/nature12624 (2013).

3 Khurana, E. *et al.* Role of non-coding sequence variants in cancer. *Nat Rev Genet* **17**, 93-108, doi:10.1038/nrg.2015.17 (2016).

4 Fujimoto, A. *et al.* Whole-genome mutational landscape and characterization of noncoding and structural mutations in liver cancer. *Nat Genet* **48**, 500-509, doi:10.1038/ng.3547 (2016).

5 Zhou, S., Treloar, A. E. & Lupien, M. Emergence of the Noncoding Cancer Genome: A Target of Genetic and Epigenetic Alterations. *Cancer Discov* **6**, 1215-1229, doi:10.1158/2159-8290.CD-16-0745 (2016).

6 Hoadley, K. A. *et al.* Multiplatform analysis of 12 cancer types reveals molecular classification within and across tissues of origin. *Cell* **158**, 929-944, doi:10.1016/j.cell.2014.06.049 (2014).

7 Torchia, J. *et al.* Integrated (epi)-Genomic Analyses Identify Subgroup-Specific Therapeutic Targets in CNS Rhabdoid Tumors. *Cancer Cell* **30**, 891-908, doi:10.1016/j.ccell.2016.11.003 (2016).

8 Consortium, E. P. An integrated encyclopedia of DNA elements in the human genome. *Nature* **489**, 57-74, doi:10.1038/nature11247 (2012).

9 O'Connor, M. L. *et al.* Cancer stem cells: A contentious hypothesis now moving forward. *Cancer Lett* **344**, 180-187, doi:10.1016/j.canlet.2013.11.012 (2014).

10 Lawrence, M. S. *et al.* Mutational heterogeneity in cancer and the search for new cancer-associated genes. *Nature* **499**, 214-218, doi:10.1038/nature12213 (2013).

11 Makova, K. D. & Hardison, R. C. The effects of chromatin organization on variation in mutation rates in the genome. *Nat Rev Genet* **16**, 213-223, doi:10.1038/nrg3890 (2015).

12 Schuster-Bockler, B. & Lehner, B. Chromatin organization is a major influence on regional mutation rates in human cancer cells. *Nature* **488**, 504-507, doi:10.1038/nature11273 (2012).

13 Polak, P. *et al.* Cell-of-origin chromatin organization shapes the mutational landscape of cancer. *Nature* **518**, 360-364, doi:10.1038/nature14221 (2015).

14 Cheng, C., Min, R. & Gerstein, M. TIP: a probabilistic method for identifying transcription factor target genes from ChIP-seq binding profiles. *Bioinformatics* **27**, 3221-3227, doi:10.1093/bioinformatics/btr552 (2011).

15 Dang, C. V. MYC on the path to cancer. *Cell* **149**, 22-35, doi:10.1016/j.cell.2012.03.003 (2012).

16 McKeown, M. R. & Bradner, J. E. Therapeutic strategies to inhibit MYC. *Cold Spring Harb Perspect Med* **4**, doi:10.1101/cshperspect.a014266 (2014).

17 Wang, D. *et al.* Loregic: a method to characterize the cooperative logic of regulatory factors. *PLoS Comput Biol* **11**, e1004132, doi:10.1371/journal.pcbi.1004132 (2015).

18 Cheng, C. *et al.* An approach for determining and measuring network hierarchy applied to comparing the phosphorylome and the regulome. *Genome Biol* **16**, 63, doi:10.1186/s13059-015-0624-2 (2015).

19 Boer, J. M. *et al.* Prognostic value of rare IKZF1 deletion in childhood B-cell precursor acute lymphoblastic leukemia: an international collaborative study. *Leukemia* **30**, 32-38, doi:10.1038/leu.2015.199 (2016).

20 Marke, R. *et al.* Tumor suppressor IKZF1 mediates glucocorticoid resistance in B-cell precursor acute lymphoblastic leukemia. *Leukemia* **30**, 1599-1603, doi:10.1038/leu.2015.359 (2016).

21 de Rooij, J. D. *et al.* Recurrent deletions of IKZF1 in pediatric acute myeloid leukemia. *Haematologica* **100**, 1151-1159, doi:10.3324/haematol.2015.124321 (2015).

22 Farh, K. K. *et al.* Genetic and epigenetic fine mapping of causal autoimmune disease variants. *Nature* **518**, 337-343, doi:10.1038/nature13835 (2015).

23 Masterson, L. *et al.* Deregulation of SYCP2 predicts early stage human papillomavirus-positive oropharyngeal carcinoma: A prospective whole transcriptome analysis. *Cancer Sci* **106**, 1568-1575, doi:10.1111/cas.12809 (2015).

24 Parris, T. Z. *et al.* Frequent MYC coamplification and DNA hypomethylation of multiple genes on 8q in 8p11-p12-amplified breast carcinomas. *Oncogenesis* **3**, e95, doi:10.1038/oncsis.2014.8 (2014).