Reviewer #1 (Remarks to the Author):

-- Reviewer 1.0 – Creating a docker image software and updating website –

@@@JL @@@JoJo

Referee Comment	0 - Neither the software nor a test instance was available for review.
Author Response	We thank the reviewer for pointing this out. We have now included a docker image at radar.gersteinlab.org which can be downloaded and installed. Included is all a test instance. Detailed instructions on installation and usage can be found at our website.
Excerpt From Revised Manuscript	

-- Reviewer 1.1 – DNA vs RNA variants, vague abstract–

@@@JZ @@@JL

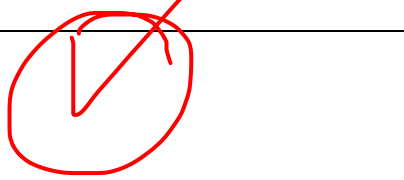
Referee Comment	1 - The abstract is vague. In my view, the authors lose a critical opportunity by not reporting the significance of previously studied cases of genetic variants that affect RBP function or how their new method can help to sort the important genetic variants from the rest (DNA vs RNA).
Author Response	We thank the reviewer for pointing this out. We agree that it should be further emphasized how genetic variants affecting RBP function are an important part of studying disease. To this end, we have revised our abstract to reflect how our method, RADAR, explores mutations in the RBP regulome and how they can be separated from mutations affecting DNA.

Excerpt From Revised Manuscript	

-- Reviewer 1.2 – Comparing RADAR, Funseq2, CADD –

@@@JZ @@@JL

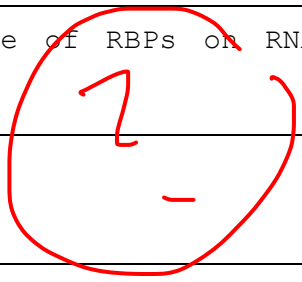
Referee Comment	2 - What is the rational to only show comparison among RADAR, FunSeq2 and CADD? See for example, https://www.ncbi.nlm.nih.gov/pubmed/29340599(A benchmark study of scoring methods for non-coding mutations). Please motivate your choice.
Author Response	The reviewer's comment here brings up a valid point. To address this concern, we have added comparisons to additional variant prioritization schemes, such as GWAVA and FATHMM-MKL.
Excerpt From Revised Manuscript	



-- Reviewer 1.3 – RBP and RNA splicing –

@@@JZ @@@JL @@@DL

Referee Comment	3 - The relevance of RBPs on RNA splicing is not considered at all.
Author Response	
Excerpt From Revised Manuscript	



-- Reviewer 1.4 – Step by step details on basic vs tissue score –

@@@JL

Referee Comment	4- The basic and tissue-specific scoring is not well explained. The method section is mixed with results (eg. In Regulatory Power from Linear Regression). Please separate results from methods. I would like to see a clear presentation on how a RADAR score is computed for a given variant from basic and user-specific contributions in mathematical terms.
Author Response	
Excerpt From Revised Manuscript	

-- Reviewer 1.5 – Relevance of features (especially non Funseq ones) –

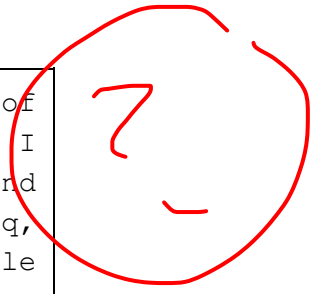
@@@JZ @@@JL

Referee Comment	5 - Please assess the individual relevance of the features listed in Table 1 for RADAR. Especially, the data types that are not modelled by the preceding software FunSeq2 (see Figure 1).
Author Response	
Excerpt From Revised Manuscript	

-- Reviewer 1.6 – K562 vs HepG2 for validation –

@@@JL @@@JZ @@@DL

Referee Comment	6 - Please use the cell-line specific aspect of ENCODE to assess the performance of your method. I believe that cell-specific information for K562 and HepG2 cell lines are available, such as shRNA-seq, eCLIP. Variant information might be also available for both cell lines as I have seen whole genome sequencing data in NCBI's SRA. Please train / build the model on one cell type ("Baseline) and evaluate on the other ("specific component"). This could be as convincing as an experimental validation.
Author Response	
Excerpt From Revised Manuscript	



-- Reviewer MINOR 1.1 – MINOR text –

@@@JL

Referee Comment	1 - page 12 line 4 - However, it is widely reported in the scientific literature that only small portion of somatic genetic variation drives cancer cells, and those passenger mutations do not affect gene function
Author Response	

Excerpt From Revised Manuscript	

-- Reviewer MINOR 1.2 – Minor; add references RBP importance –

@@@JL

Referee Comment	2 - page 13 line 29 - This claim is not useful without a gold-standard dataset, begging for the question: what is the specificity of the RADAR score? How does it look for genes that are not as well studied in cancer?
Author Response	
Excerpt From Revised Manuscript	

-- Reviewer MINOR 1.3 – Minor comment –

@@@JL

Referee Comment	3- Supl 2.1: pvrect function from pvclust package
Author Response	

Excerpt From Revised Manuscript	

Reviewer #2 (Remarks to the Author):

-- Reviewer 2.0 – Relative size of RBP Regulome –

@@@JL @@@JZ

Referee Comment	One major concern appears to be whether the observed results are reflective of true biology or simply artifacts of various algorithms. For example, figure 2 and lines 21-32 discuss the overlap between eCLIP peaks and annotations. However, the description of the CLIPper algorithm in Lovci et al (2013) used in the ENCODE pipeline suggests that clusters are identified only within transcripts, which would then trivially localize all eCLIP peaks to transcript annotations. Similarly, although the 'RBP regulome' appears smaller than that for TFs, it is unclear whether this is simply because the average peak size for eCLIP is significantly smaller than the average CHIP-seq peak due to differences in method and peak callers (likely, as most known RBP and TF motifs are of similar sizes).
Author Response	
Excerpt From Revised Manuscript	

-- Reviewer 2.1 – Narrow vs Broad scope binding eCLIP peaks –

@@@JL @@@JZ

Referee Comment	One major question regards the weighting of eCLIP binding sites. The eCLIP data appears to contain not only narrow binding proteins, but also broad binding or coating proteins (such as POLR2G https://www.encodeproject.org/experiments/ENCSR820WHR/). Perhaps because of this, the number of significant peaks appears to range dramatically between datasets, from less than a hundred to tens of thousands. Similarly, knockdown of some proteins which are essential cause dramatically more gene expression changes than others. It is unclear from the manuscript how these are differently weighted in the end, and thus whether RADAR is simply reflecting predictions of a small number of broadly binding RBPs.
Author Response	
Excerpt From Revised Manuscript