Exploring the RNA Editing Landscape of Metastatic Prostate Cancer

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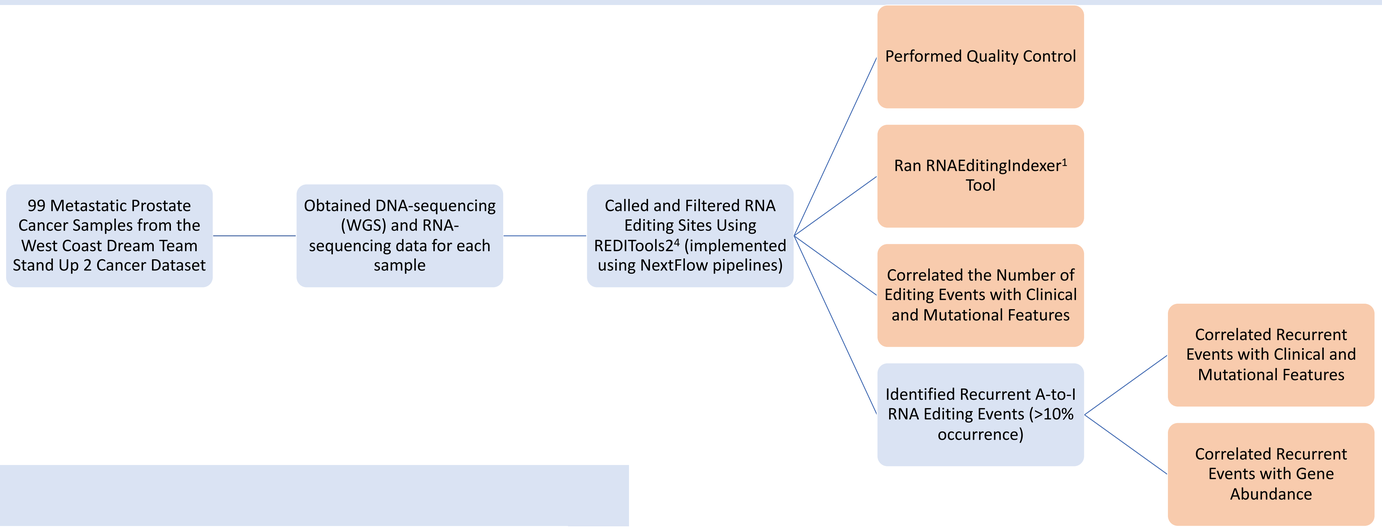
Abstract

RNA editing is a post-transcriptional mechanism affecting both protein-coding transcripts and non-coding transcripts. The most common modification is adenosine-to-inosine (A-to-I) editing, which is frequently more active in cancer cells, and mediated by the ADAR1 enzyme[1]. A-I editing can introduce non-synonymous mutations, resulting in protein heterogeneity[2], but the nature and functional consequences of these changes in cancer remain widely unexplored. To characterize the landscape of A-to-I RNA editing in prostate cancer, we identified A-to-I RNA editing sites across 99 publicly available metastatic tumours[3] using both RNA-sequencing and DNA-sequencing data. We then investigated associations between A-to-I RNA editing and key clinical and genomic features. We discovered that A-to-I editing sites were significantly associated with changes in gene abundance. An exploration of A-to-I RNA editing in metastatic prostate cancer, combined with future exploration of localized tumours, may identify candidate RNA editing sites that contribute to protein heterogeneity in prostate cancer.

Methods



Results

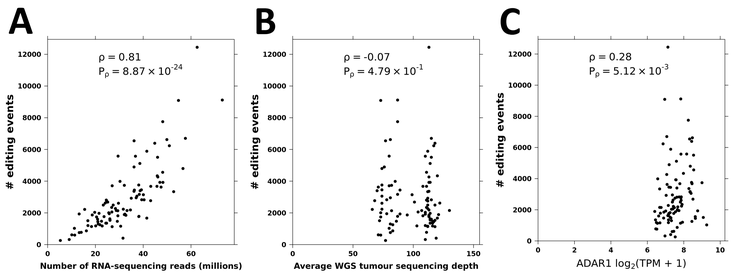


Figure 1. Quality Control. Associations between (A) number of RNA-sequencing reads, (B) average WGS tumour sequencing depth, and (C) ADAR1 abundance with number of editing events. Spearman's ρ and P-values are shown.

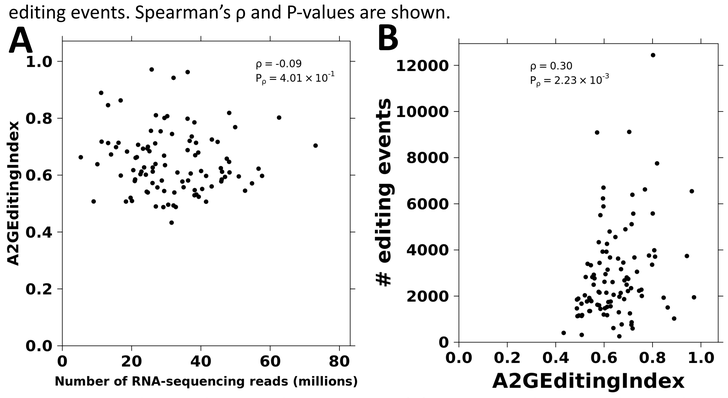


Figure 2. RNAEditingIndexer Tool Comparison. (A) Association between the number of RNA-sequencing reads and the RNAEditingIndexer[1] A2GEditingIndex output. The A2GEditingIndex quantifies the amount of ADAR activity across each sample, and is robust to differences in coverage. (B) Association between A2GEditingIndex and number of editing events. Spearman's ρ and P-values are shown.

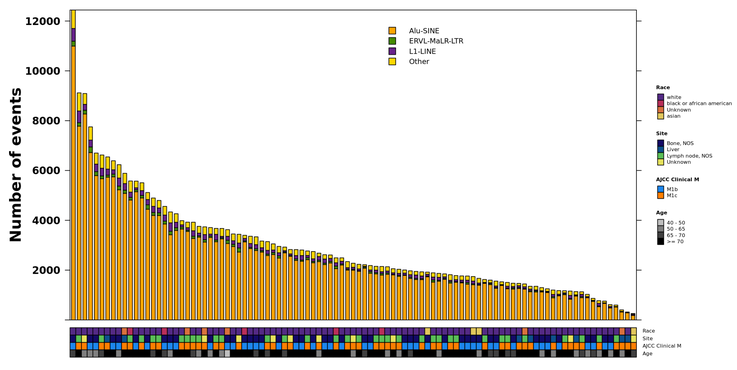


Figure 3. **Landscape of RNA A-to-I editing events**. The distribution of editing events colored by the annotation across Alu-SINE, ERVL-MaLR-LTR, L1-LINE, and other genomic elements. There were no significant associations between the number of editing events and clinical covariates (Kruskal-Wallis test for race and metastasis site, Mann-Whitney U test for AJCC Clinical M, and Spearman's correlation for age). *may need to be updated based on correspondence with the dataset authors.*

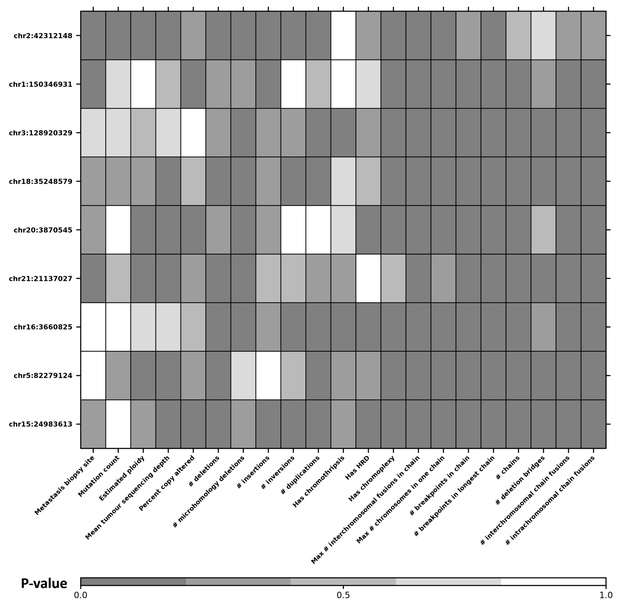


Figure 4. Recurrent event associations with genomic features. Association tests (Kruskal-Wallis for metastasis biopsy site, Mann-Whitney U test for chromothripsis, HRD, and chromoplexy, and Spearman's correlation for the remaining features) reveal no significant associations with recurrent A-to-I editing sites after FDR correction. 9 RNA A-to-I editing sites show significant associations ($p < 0.05$) before FDR correction with 10 or more genomic features.

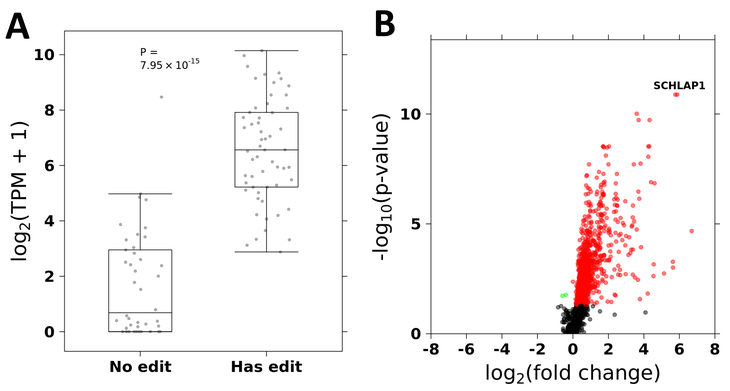


Figure 5. Recurrent event associations with gene abundance. (A) Association between RNA editing status and gene abundance at position chr2 180,916,757, located in the SCHLAP1 gene locus. SCHLAP1 is a long non-coding RNA found to be upregulated in prostate tumours[5]. Mann-Whitney U test P-value is shown. (B) Volcano plot displaying the fold change and FDR-adjusted P-values for Mann-Whitney U tests between recurrent A-to-I editing event frequencies and their corresponding gene abundance. After FDR correction, 1112 sites were significantly upregulated gene abundance and 2 sites significantly downregulated gene abundance.

Future Work

- Explore proteomic effects of RNA A-to-I editing by associating editing sites and alternative splicing
- Perform complementary analysis with RNA editing in localized prostate cancer samples
- Compare RNA editing landscape in localized and metastatic prostate tumours

References

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