

Reviewer Report

Title: Mutation Impact on mRNA Versus Protein Expression across Human Cancers

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Reviewer Comments to Author:

The manuscript "Mutation Impact on mRNA Versus Protein Expression across Human Cancers" investigates how somatic mutations affect mRNA and protein expression using data from 953 cancer cases across six types. The study identifies that 47.2% of mutations impacting mRNA levels (seQTLs) also affect protein levels, validating their broader impact. A novel statistical method uncovers 83 protein-specific QTLs (spsQTLs), primarily truncating mutations, significantly affecting protein abundance. Functional validation confirms TP53 missense mutations with high protein levels are functional. However, my main concern is the relationship between mRNA expression and protein expression. The low correlation between these two levels may undermine the analysis, suggesting different regulatory mechanisms. If low correlation is observed, the overlap between seQTL and spQTL may lack biological significance. Also, truncating mutations reducing protein expression seems straightforward, but this does not fully address the complex regulation mechanisms. Therefore, I suggest that the authors first compare the correlation between mRNA and protein expression and select cancer types that show high correlation for subsequent analyses. This approach would provide a more robust biological foundation for the study.

Methods

Are the methods appropriate to the aims of the study, are they well described, and are necessary controls included? Choose an item.

Conclusions

Are the conclusions adequately supported by the data shown? Choose an item.

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