Reviewer Report

Title: Proteome-wide association study and functional validation identify novel protein markers for pancreatic ductal adenocarcinoma

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Reviewer name: Huang Peng

Reviewer Comments to Author:

Zhu et al. constructed a series of pQTL models and used them to identify genetic predicted serum protein markers for pancreatic ductal adenocarcinoma, followed by a series of functional validations, which may provide valuable clues for prediction and treatment of PDAC. I have several concerns on this study.

Major concerns:

1. This study integrated both cis- and trans-acting elements to construct pQTL models. It would be better to provide the heritability of each pQTL model constructed and the comparison results (such as the h2 explained and predictive performance on gene expression) with those focus solely on cis-acting variants, as the author stated that the integration strategy has an enhanced statistical power.
2. The integration strategy is somewhat like some PGS methods (such as C+T). Would the author consider to try some other strategies used in common PGS analysis? For example, using LD clumping for SNPs selection, trying some other P value threshold combinations to define and select gene- associated SNPs in cis and trans regions, and using the bslmm strategy, which seems to be demonstrated to have decent performance in the FUSION article.
3. This study selected proteins for pWAS analysis based on prediction R/R2 of pQTL models. Would the author take the h2 of each pQTL model into consideration as the FUSION article did?
4. Although the author used the TWAS/FUSION framework for pQTL models construction and protein-PDAC association assessment, it would be better to add more description into the supplementary file on how this framework was applied to the current 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.

Reporting Standards

Does the manuscript adhere to the journal’s guidelines on minimum standards of reporting? Choose an item.

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Statistics

Are you able to assess all statistics in the manuscript, including the appropriateness of statistical tests used? Choose an item.

Quality of Written English

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