**Reviewer's report**

**Title:** Protein modeling to assess the pathogenicity of rare variants of SERPINA1 in patients suspected of having Alpha 1 Antitrypsin Deficiency

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**Reviewer:** Shantel Weinsheimer

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Kueppers et al. presents a well-written report summarizing their evaluation of the utility of computational modeling to provide supporting evidence regarding the pathogenicity of novel SNPs in the SERPINA1 gene. For a total of 23 patients suspected of having Alpha 1 Antitrypsin deficiency they used NGS and predictive computational analyses, in addition to quantification of serum AAT levels and qualitative analysis by isoelectric focusing, to identify mutations in SERPINA1. Using 3 predictive methods, SVM, FoldX and PolyPhen-2, they categorized the identified mutations as probably deleterious, possibly deleterious, possibly neutral, or probably neutral. The authors also present a benchmarking analysis of SVM predictions against three datasets of known SERPINA1 pathogenic and benign variants from ClinVar.

The study methods are clearly presented and elaborated in the supplementary material. The results are well-written and the key findings of 21 rare/novel mutations identified were presented in detail. The authors provide an important description of how the mutations may result in corresponding AAT levels, especially in the context of combination with more common deficiency alleles. The authors point out a few important limitations such as the fact that this is an observational study and not a controlled study and that they do not report on additional genetic or non-genetic factors that could contribute to the development of the clinical phenotype (COPD).

The conclusions are well supported and suggest that NGS and computational modeling, especially the SVM method, are useful tools to identify important mutations in SERPINA1 that may aid the diagnosis of AATD and lead to improved clinical care for individuals harboring these mutations.

Additional points for the authors to consider:

1) Given that AAT inhibits eg. elastase, is there any information on mutations in the elastase gene in these patients that would also influence the progression to the clinical phenotype? For example, mutations in elastase that affect the ability for AAT to inhibit properly?

2) Is there any additional information regarding presentation of cerebral aneurysm or family history of aneurysm in the patients? ie. were all patients screened for cerebral aneurysms?

3) Are there any cellular or animal models that support that there is an altered functional activity and/or protein levels for the specific SERPINA1 mutations presented in this report?
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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Please indicate the quality of language in the manuscript:

Acceptable

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