Reviewer's report

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

Version: 0 Date: 07 Feb 2019

Reviewer: Guy Lenk

Reviewer's report:

This paper describes the use of computational analyses to understand the growing number of variants of unknown significance (VUS) in genetic disease etiology. With the application of genome and exome sequencing to ascertain the genetic causes behind these diseases this is a problem that is likely to grow. The authors have focused on alpha 1 antitrypsin deficiency (AATD) which is a well recognized disease with multiple clinical phenotypes and this paper uses a cohort that is well described. The analytical methods employed in the paper take into account all aspects known regarding SERPINA1 and don't solely rely on any one metric. This paper is well written and well described and furthers the understanding of the clinical spectrum of genetic variants in AATD. Additionally the critical need for early and accurate diagnosis of AATD is meaningfully pointed out by the authors.

One minor point:

The word mutations is used when variants is likely to be what the authors meant (such as p4;line 59 - p5;line 80 - p5;line 84 - p6;line 109 - etc). If these are suspected to be de novo (i.e. mutations) for some reason that should be more clear, otherwise the authors should consider using more general terminology (e.g. variant).

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

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license ([http://creativecommons.org/licenses/by/4.0/](http://creativecommons.org/licenses/by/4.0/)). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal