LAKSMI WULANDARI <laksmi.wulandari@fk.unair.ac.id>

FW: Confirmation of your submission to Human Genomics - HUGM-D-21-00038

Delvac Oceandy <Delvac.Oceandy@manchester.ac.uk> 2 Maret 2021 20.20
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Cc: Cennikon Pakpahan <cennikon@gmail.com>, "monicarizkyw@gmail.com" <monicarizkyw@gmail.com>, hamidah Berliana <berliana-hamidah@fk.unair.ac.id>

Dear All

I've submitted manuscript on TMPRSS2 to BMC Human genomics. Please see attached MS as submitted. I've opted in to Springer Nature In Review facility (https://www.springernature.com/gp/authors/campaigns/in-review) to enable early sharing and pre-print. Hope it's OK with everybody.

Best wishes
Delvac

-----Original Message-----
From: em.hugm.0.71af6d.2ef118f4@editorialmanager.com <em.hugm.0.71af6d.2ef118f4@editorialmanager.com> On Behalf Of Human Genomics Editorial Office
Sent: 02 March 2021 13:07
To: Delvac Oceandy <Delvac.Oceandy@manchester.ac.uk>
Subject: Confirmation of your submission to Human Genomics - HUGM-D-21-00038

HUGM-D-21-00038
Initial Study on TMPRSS2 p.Val160Met Genetic Variant in COVID-19 patients Laksmi Wulandari; Berliana Hamidah; Cennikon Pakpahan; Nevy Shinta Damayanti; Neneng Dewi Kurniati; Christophorus Oetama Adiatmaja; Monica Rizky Wigianita; Soedarsono Soedarsono; Dominicus Husada; Damayanti Tinduh; Cita Rosita Sigit Prakoeswa; Anang Endaryanto; Ni Nyoman Tri Puspaningsih; Maria Inge Lusida; Kazufumi Shimizu; Delvac Oceandy Human Genomics

Dear Dr Oceandy,

Thank you for submitting your manuscript 'Initial Study on TMPRSS2 p.Val160Met Genetic Variant in COVID-19 patients' to Human Genomics.

The submission id is: HUGM-D-21-00038
Please refer to this number in any future correspondence.

During the review process, you can keep track of the status of your manuscript by accessing the following website:

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Best wishes,

Editorial Office
Human Genomics
https://humgenomics.biomedcentral.com/

The Editorial Office perform a basic check of your manuscript at initial submission so it may proceed to peer review. Please note, there may be additional technical requirements for your manuscript based on the Submission Guidelines on the journal website - these would be requested at a later stage (if your manuscript requires editorial revisions, or prior to publication).

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HUGM-S-21-00049.pdf
1519K

LAKSMI WULANDARI <laksmi.wulandari@fk.unair.ac.id>

FW: Your submission to Human Genomics - HUGM-D-21-00038

Delvac Oceandy <Delvac.Oceandy@manchester.ac.uk> 20 Maret 2021 19.02
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Dear All

Below is the decision for the TMPRSS2 paper. think it's manageable. Will discuss with core group to address rev comments.

Best wishes
Del

-----Original Message-----
From: em.hugm.0.721036.940d1c60@editorialmanager.com <em.hugm.0.721036.940d1c60@editorialmanager.com>
On Behalf Of Human Genomics Editorial Office
Sent: 19 March 2021 17:04
To: Delvac Oceandy <Delvac.Oceandy@manchester.ac.uk>
Subject: Your submission to Human Genomics - HUGM-D-21-00038

HUGM-D-21-00038
Initial Study on TMPRSS2 p.Val160Met Genetic Variant in COVID-19 patients Laksmi Wulandari; Berliana Hamidah; Cennikon Pakpahan; Nevy Shinta Damayanti; Neneng Dewi Kurniati; Christophorus Oetama Adiatmaja; Monica Rizky Wigianita; Soedarsono Soedarsono; Dominicus Husada; Damayanti Tinduh; Cita Rosita Sigit Prakoeswa; Anang Endaryanto; Ni Nyoman Tri Puspaningsih; Maria Inge Lusida; Kazufumi Shimizu; Delvac Oceandy Human Genomics

Dear Dr Oceandy,

Your manuscript "Initial Study on TMPRSS2 p.Val160Met Genetic Variant in COVID-19 patients" (HUGM-D-21-00038) has been assessed by our reviewers. Although it is of interest, we are unable to consider it for publication in its current form. The reviewers have raised a number of points which we believe would improve the manuscript and may allow a revised version to be published in Human Genomics.

Their reports, together with any other comments, are below. Please also take a moment to check our website at https://www.editorialmanager.com/hugm/ for any additional comments that were saved as attachments.

If you are able to fully address these points, we would encourage you to submit a revised manuscript to Human Genomics. Once you have made the necessary corrections, please submit online at:

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Please include a point-by-point response within the 'Response to Reviewers' box in the submission system and highlight (with 'tracked changes'/coloured/underlines/highlighted text) all changes made when revising the manuscript. Please ensure you describe additional experiments that were carried out and include a detailed rebuttal of any criticisms or requested revisions that you disagreed with. Please also ensure that your revised manuscript conforms to the journal style, which can be found in the Submission Guidelines on the journal homepage.

The due date for submitting the revised version of your article is 18 Apr 2021.

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I look forward to receiving your revised manuscript soon.

Best wishes,

Giuseppe Novelli, Prof.
Human Genomics
https://humgenomics.biomedcentral.com/

Reviewer reports:

Reviewer #1: Wulandari et al. investigated the association between the genetic variant p.Val160Met in TMPRSS2 coding region, and the severity, viral load and clinical outcomes of COVID-19 patients. They observed an association between this genetic variant and the viral load in COVID-19 patients.

I have the following comments and questions for the authors:

1) The authors speculate that genetic variability within the TMPRSS2 gene may play a role in SARS-CoV-2 infection. To better investigate this hypothesis, it would be advisable to evaluate the entire gene, or at least to examine other polymorphisms located in TMPRSS2 gene. If that is not possible, the authors should explain in the introduction why only this genetic variant was chosen.

2) In order to evaluate a possible association of the genetic variant with the disease severity, it would also be correct to analyze a group of asymptomatic patients.

3) The authors observed a deviation from Hardy Weinberg equilibrium for the p.Val160Met in polymorphism in all patients. How do they explain this data? Is the frequency of the variant allele found in the group analyzed comparable to that of the general population?

4) A significant difference was observed in the Ct value between patients with a TT genotype and patients with a CC genotype. Did they assess whether other factors such as gender, age, or clinical characteristics are related to the Ct value?

5) The genetic variant p.Val160Met in TMPRSS2 was analyzed in different studies on COVID-19 patients. It would be appropriate to broaden the discussion by mentioning the relevant literature.

6) A functional study in culture cells could confirm the effect of the variant on the structure or function of the protein. Because these data cannot be easily investigated, I think that it would be appropriate that the authors mention this limitation in the Discussion.

Reviewer #2: Wulandari and et al. investigate the genetic association between TMPRSS2 p.Val160Met SNP (rs12329760) and different clinical manifestations of COVID-19. The authors found no association of this SNP with disease severity, but they observed a significant association with viral load. Particularly they report that the C allele significantly correlated with high viral load and was more frequent among people that died of COVID-19 if affected by a severe disease.
The topic is relevant as GWAS, WES and candidate gene studies have already demonstrated that common and rare variants can influence the risk of developing a severe COVID-19. Moreover, the C allele of p.Val160Met has been already reported as risk factor in recent papers(https://doi.org/10.3390/genes11091010, https://doi.org/10.1016/j.isci.2021.102322
and DOI: 10.1038/s41421-020-00231-4)
However, the manuscript in this form present diverse flaws that need to be addressed.
Major Concerns
I suggest redoing the statistical analysis grouping mild and moderate against severe patients.
The ORs and CI should be included in Table 3 and Table 4.

The table 2 is redundant and should be eliminated.

A recent published paper found the C allele (rs12329760) is more frequent in 131 SARS-COV-2 positive patients when compared to European Gnomad data (Genes 2020, 11(9), 1010; https://doi.org/10.3390/genes11091010) and another paper reports that the same allele predispose to increased risk of developing severe COVID-19 when analyzing different cohorts of cases and controls with different ethnic origin (https://doi.org/10.1016/j.isci.2021.102322). These findings are partially in accord whit the conclusion of this article and thus should be commented in discussion section.
Finally, I suggest interrogating the GWAS release 5 of the HIG database (https://app.covid19hg.org/) to test if the allele C of rs12329760 is associated with diverse clinical manifestations of COVID-19 in this international study.

Technical Comments from the Editorial Office:

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