

## Jury Member Report – Doctor of Philosophy thesis.

**Name of Candidate:** Vita Stepanova

**PhD Program:** Life Sciences

**Title of Thesis:** Methabolic variations of modern and ancient human populations

**Supervisor:** Prof. Philipp Khaitovich

**Date of Thesis Defense:** 20 December 2019

**Name of the Reviewer:** Eva Schulte

<p>I confirm the absence of any conflict of interest</p> <p>(Alternatively, Reviewer can formulate a possible conflict)</p>	<p><b>Signature:</b></p> <p><i>Eva C. Schulte</i></p> <p><b>Date: 09-12-2019</b></p>
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*The purpose of this report is to obtain an independent review from the members of PhD defense Jury before the thesis defense. The members of PhD defense Jury are asked to submit signed copy of the report at least 30 days prior the thesis defense. The Reviewers are asked to bring a copy of the completed report to the thesis defense and to discuss the contents of each report with each other before the thesis defense.*

*If the reviewers have any queries about the thesis which they wish to raise in advance, please contact the Chair of the Jury.*

### Reviewer's Report

Reviewers report should contain the following items:

- Brief evaluation of the thesis quality and overall structure of the dissertation.
- The relevance of the topic of dissertation work to its actual content
- The relevance of the methods used in the dissertation
- The scientific significance of the results obtained and their compliance with the international level and current state of the art
- The relevance of the obtained results to applications (if applicable)
- The quality of publications

The summary of issues to be addressed before/during the thesis defense

#### 1) Quality and overall structure

Ms Stepanova presents an extensive thesis with reasonable overall structure. She assesses multiple aspects of lipidomics and metabolomics in the context of different modern and ancient human populations. The analyses performed are very comprehensive and of high quality and span a broad methodological spectrum.

#### 2) Relevance of actual content to topic

The overall content of the thesis work is very relevant to the topic. The candidate presents analyses comprehensively assessing different facets of the chosen topic by looking at both population- and modern-human-specific aspects of metabolomics and lipidomics. She also presents analyses attempting to assess the functional relevance of identified differences between modern- and ancient human populations. The focus on brain tissue and the CNS also seems very relevant as that—at least with regard to the differences between modern and ancient humans—presents the organ most likely to harbor the most relevant and the most consequential differences.

#### 3) Relevance of methods

Overall the methods used are very diverse ranging from machine learning and in-depth statistical analyses to metabolomics and lipidomics all the way to transgenic mouse models. I am unable to assess the statistical evaluations in full detail, however, the remaining methods are very appropriate and are used appropriately. A number of the methods presented (i.e. cell-culture and mouse models) were not performed by the candidate herself. While she nicely differentiates between the experiments performed by herself and those performed by others, to me it seems unnecessary to present the methods she did not perform in extensive detail.

#### 4) Scientific significance ? State of the art and accordance with international standards ?

As illustrated by the publication record, the results are of high scientific significance. The thesis assesses fundamental questions about the differences between human populations as well as the differences between modern and ancient humans. These differences are also important in the context of gaining a better understanding of disease pathomechanisms. The experiments and analyses performed are state of the art and fully meet international standards.

#### 5) Relevance of results for future applications ?

As described by the candidate in the conclusion, the studies depicted are remarkable in that they span a broad spectrum from the identification of lipidomic/metabolomics changes to performing functional follow-up studies. As such the present a blueprint for similar studies to follow in the future.

#### 6) Quality of publications ?

Ms Stepanova provides a publication list that lists six publications. Three of these six do not seem to be directly related to the thesis work presented herein but are probably related to work performed by the candidate before the start of the PhD project. Ms Stepanova is a co-author/middle author on five of the six publications and the shared first author on the sixth. All six publications were published in well-reputed journals with one from the current PhD project and one from prior work published in high-visibility journals such as *Genome Research* and *PNAS*. It remains unclear, if there are more publications currently in preparation. Although a second first-authorship would be desirable, this has become ever more difficult in the quotidian, highly-collaborative scientific environment.

7) Issues to be addressed

- please remove cyrillic parts of Table of Content
- please double check citation format (e.g. page 20 middle of the page: How many authors are given for each publication ? Are first name initials included ?)
- please add the relevant data/results for the stability analysis of ADSL to the relevant paragraph on p. 42; it feels like there is something missing.

**Provisional Recommendation**

*I recommend that the candidate should defend the thesis by means of a formal thesis defense*

*I recommend that the candidate should defend the thesis by means of a formal thesis defense only after appropriate changes would be introduced in candidate's thesis according to the recommendations of the present report*

*The thesis is not acceptable and I recommend that the candidate be exempt from the formal thesis defense*