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Jury Member Report – Doctor of Philosophy thesis.

Name of Candidate: Vita Stepanova

PhD Program: Life Sciences

Title of Thesis: Metabolic variations of modern and ancient human populations

Supervisor: Prof. Philipp Khaitovich

Date of Thesis Defense: 20 December 2019

Name of the Reviewer: Georgii A. Bazykin

I confirm the absence of any conflict of interest	**Signature:**  **Date: 06-12-2019**

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

The thesis addresses the important topic of differences in metabolite and lipid concentrations between human populations, and between humans and other species. Using state-of-the-art methods for assessment of molecular phenotypes and data analyses, the author reveals differences in metabolite concentrations between the Han Chinese and other analyzed populations. At the interspecies level, she also identifies the derived differences in metabolism that had occurred at the human lineage after its divergence from the Neanderthals. Finally, she identifies and analyzes a particular amino acid substitution that is apparently responsible for a change in purine biosynthesis, and discusses its biological role. These results are among the first population- and interespecies-level metabolic reconstructions, and the analysis is of very high quality; therefore, I believe these results to be of very high significance.

The thesis includes 6 chapters; chapter 3, which carries the bulk of the results, includes two parts. The first part has been published as a paper in *Scientific reports,* on which Vita is a joint first author. Vita also has coauthored many papers on related topics that didn't make it into the body of the thesis.

The thesis is a pleasure to read; all data and analyses are clearly described, the limitations of the analyses are adequately acknowledged, and the results are summarized in very high-quality figures. There are very few typos and inaccuracies.

I have just a few comments that I would like to see addressed before or at the defense.

1. In pp. 26–27, two distinct ways are used to calculate the number of lipids differing between the HC and the other two populations: one yields 90 lipids (p. 26), while the other yields 395 lipids (p. 27). Similarly, the two analyses for metabolites yield 93 or 166 HC-specific differences. I was confused by the differences between these approaches, and the causes of these 2- or 3-fold differences between types of analyses; please clarify them.

2. As explained in p. 34, the analysis of changes in metabolome specific to the human lineage uses differences between modern humans and the chimpanzee-macaque pair. This basically assumes parsimony: if chimp and macaque are indistinguishable, but different from the humans, it is inferred that one change has happened in the human lineage, as opposed to one change in each of the chimp and macaque lineages. For genetic changes, this assumption is certainly valid, as the genetic distances between the species are low (~1% between human and chimp, ~5% between human and macaque) and repeated changes are unlikely. By contrast, previous work, including some from the same lab, has shown that metabolites evolve in a non-clocklike fashion. Can the violation of parsimony assumptions lead to erroneous inference of the direction in metabolome changes?

Provisional Recommendation

X *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*