Skoltech

Skolkovo Institute of Science and Technology

Jury Member Report – Doctor of Philosophy thesis.

Name of Candidate: Vita Stepanova

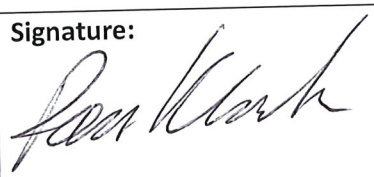
PhD Program: Life Sciences

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

Supervisor: Prof. Philipp Khaitovich

Date of Thesis Defense: 19 December 2019

Name of the Reviewer: Peter Kharchenko

I confirm the absence of any conflict of interest (Alternatively, Reviewer can formulate a possible conflict)	**Signature:**  **Date: 01-12-2019**

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
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

The dissertation presents analysis of variation of lipid and metabolite content within human population, as well as between humans, primates and rodents. The study emphasizes the analysis of the cortical regions, and dives into the mechanism potentially accounting for the human-specific difference in purine metabolism. The dissertation is well-written and follows a clear logical structure.

Our brains consist mostly of lipids. These lipids serve both structural and signaling roles, and their balance is known to be essential for brain development and function. While shifts in the lipid and metabolite composition of the brain have been linked to a variety of neuropseychiatric disorders and cognitive dysfunction, the overall organization and specific functional roles of different lipids remain poorly characterized. In particular, much remains unclear about the processes regulating lipid composition, as well as the mechanisms by which many specific lipids or metabolites contribute to brain function. The presented dissertation significantly expands on the existing efforts to characterize variation of lipid and metabolite composition within human population, as well as between humans, primates and other mammals. Specifically, the study shows significant age-dependent lipid and metabolome difference in the Han Chinese compared to Western European and African American populations. To gain wider perspective, the dissertation goes on to examine the differences between species, comparing humans with monkeys and apes, and noting persistent downregulation of purine metabolism in humans across tissues. The study then dices into characterization of a human-specific mutation in a gene encoding a key enzyme in the purine metabolism, examining mouse and cell line constructs. Some analysis of metabolome differences in the autism cases is also presented, though this part lacks detail.

The presented work, in my opinion, represents a notable step towards improved characterization of how lipid and metabolite composition of the brain and other organs varies within human population and mammalian evolution in general. It provides more specific hypothesis about the causal mechanisms and functional impacts of such variation. The presented statistical and computational anlaysis, which was the primary responsibility of the dissertation author, is relatively standard, but is well suited for the questions being posed. The author's contribution to this line of research is reflected in several recent publications, including a 'co-first' authorship in a manuscript describing the core of the disseratation, now accepted for publication in Scientific Reports.

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*