Skoltech

Skolkovo Institute of Science and Technology

Jury Member Report – Doctor of Philosophy thesis.

Name of Candidate: Ilia Kurochkin

PhD Program: Life Sciences

Title of Thesis: Comparative analysis of human brain based on mass-spectrometry data

Supervisor: Prof. Philipp Khaitovich

Chair of PhD defense Jury: Prof. Mikhail Gelfand   *Email*: m.gelfand@skoltech.ru

Date of Thesis Defense: 26 October 2018

Name of the Reviewer: Prof. Andrey Mironov

I confirm the absence of any conflict of interest (Alternatively, Reviewer can formulate a possible conflict)	Signature: Date: 08-10-2018

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

- Brief evaluation of the thesis quality and overall structure of the dissertation.

The presented work is devoted to the study of brain metabolism in healthy people and people suffering from various cognitive disorders. The work is part of a large project and it mainly deals with the bioinformatics aspects of this problem. The structure of theses has a standard structure. The summary gives a brief description of the work. In the introduction given the formulation of the problem. A review of the literature on the topic of work includes papers on the genetics and metabolomics of neurological disorders. Particular attention is paid to the metabolomics of lipids in normal and in disorders. Work related to the evolution of transcriptomes and metabolomes is also reviewed. Here, it is rather reasonable to speak not about evolution, but about selection pressure. Chapters 3,4,5, devoted to the description of the results have an internal structure, which includes sections on materials and methods, the actual results and discussion. The thesis is well written, all the observations are supported with statistical analysis and appropriate plots. In general, the work makes a very positive impression.

- The relevance of the topic of dissertation work to its actual content

The title of the thesis fully reflects its content. Chapter 3 analyzes the Metabolome signature of autism in the human prefrontal cortex. The materials and methods section describes the main sources of biomaterials, the methods used for mass spectrometry, as well as methods for statistical analysis of results. It would seem to me reasonable to describe the description of mass spectrometry methods in the literature review, and in the chapter on the results simply should give the appropriate reference, since the author did not conduct mass spectrometry experiments himself.

The next chapter (4) is devoted to Lipidome alterations in human prefrontal cortex in cognitive disorders. Unlike the previous chapter, here the author concentrated on the membrane lipid composition.

In the final chapter 5 of the results, the author explores the evolutionary aspects of lipidomics.

- The relevance of the methods used in the dissertation

Various methods of statistical processing of results and machine learning approaches were used and interesting results were obtained. In chapter 3 the author uses F-test, which is applicable only for normally distributed random variables. However, verification of data normality is not performed. Usually, it means that the p-values may be biased. Here the author used PCA to visualize the results, although the t-sne method is currently very popular. In chapter 4, other, more correct, statistical methods based on the Wilcoxon test and permutations are used. In chapter 5 samples from different tissues were analyzed. Here, however, it should be noted that in the analysis of lipidome mass spectrometry data is used, which are qualitative rather than quantitative. When interpreting the data, one should understand that lipids participate in the construction of a large number of different membranes - the outer cell membrane, the axon, and synapse membrane, as well as a large variety of intracellular membranes (ER, Golgi apparatus, etc.). Moreover, the work used data from different sources. This means that artifacts associated with the characteristics of laboratories are possible. It would be useful to compare data from different laboratories obtained for the same types of biomaterials.

- The scientific significance of the results obtained and their compliance with the international level and current state of the art

The subject of this thesis related to the very new field of science. In chapter 3 the statistical analysis of the data allowed the author to find from among 1366 metabolites only 202 of those associated with autism. These metabolites are involved in only 16 metabolic pathways. I find this observation very interesting. Further, the author compared metabolic data with data on gene expression and showed good agreement, which is an additional confirmation of the results obtained. As a result, a number of new metabolites associated with the development of autism were found. In chapter 4, the author finds several lipids, the lack of which is associated with disorders such as schizophrenia and autism. In chapter

5 the lipid composition of different tissues for several species was analyzed. The most interesting result is the strong difference in lipid composition in the human line. One of the important results is that changes in the lipid composition respond better to the phenotype than the level of gene expression. Nevertheless, this may be a result of data being obtained from different laboratories.

- The relevance of the obtained results to applications (if applicable)
- The quality of publications

Unfortunately, only one article has been published, another article has been accepted for publication, but has not been published. In these articles, Kurochkin is not the first author, which can be understood given the scale of the entire project. An article devoted to the study of autism, in which Kurochkin is the first author, is just preparing for publication.

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*