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Jury Member Report – Doctor of Philosophy thesis.

Name of Candidate: Aleksei Mironov

PhD Program: Life Sciences

Title of Thesis: Tissue-specificity and regulation of aberrant alternative splicing

Supervisor: Assistant Professor Dmitri Pervouchine

Name of the Reviewer: Philipp Khaitovich

I confirm the absence of any conflict of interest	**Date: 02-09-2022**

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

This PhD thesis represents a large-scale systematic analysis of two types of splicing events, tandem alternative splice sites and unproductive splicing events. The analysis is based on a large public high-coverage gene expression dataset (GTEx) containing data from multiple human tissues, including several brain regions. The dissertation focus is very clear and addresses analytically challenging but biologically important research topic. The methods used in data analysis and assessment are top-notch and fully appropriate for the task. The data analysis includes comparison of the splicing events with gene and protein expression data, and splicing analysis itself includes multiple comparisons taking advantage of the information-rich source dataset. These analyses enable author to relate his finding with reported biological processes and formulate novel and biologically relevant hypotheses regarding the role of identified splicing events in tissue biology, and suggest potential regulatory roles of known RNA-binding proteins. The examples of tissue-specific TASS provided in the thesis are also very impressive and illustrative. The scientific quality of the thesis is undoubtfully high and the scientific significance of the results is at the best international level, as reflected by the high quality of resulted publication.

The thesis is very well written, both the informative introductory part, which is also very well illustrated, and the results part, including all the methodological and analytical details and appropriate figures and detailed

figure legends. The thesis objectives are well formulated and the results and conclusions fully match them. Overall, the thesis is very nicely formatted, showing substantial attention to details.

The small points what could be considered by the author (not obligatory):

- page 20: “Approximately 95% of mammalian genes are susceptible to AS [20], which strongly influences transcriptome and proteome diversity [21, 22] and pro- vides additional layers of gene expression regulation [13].” – while this statement is certainly correct for the transcriptome, the effect of AS on the proteome diversity is not as extensive, as many splice variants do not affect the protein coding region.
- tissue-specific TASS: while definition of these events is clearly described in the methods and the examples are also clear, some of the patterns could be considered as tissue-dependent, rather than tissue-specific. The same seems to be the case for unproductive splicing events. This point does not affect the importance and correctness of results, on the opposite – it shows that splicing events with more complex patterns than single-tissue specificity are also included in the analysis.
- More parallels of obtained results with the tissue specificity of other types of splicing events, for instance their prevalence in brain, skeletal and heart muscle, as well as their regulation specificity across tissues could have been mentioned in the Discussion section.

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*