

## Jury Member Report – Doctor of Philosophy thesis.

**Name of Candidate:** Mikhail Moldovan

**PhD Program:** Life Sciences

**Title of Thesis:** Heritable modifications of transmitted biological information as possible sources of adaptation

**Supervisor:** Professor Mikhail Gelfand

**Name of the Reviewer:** Assistant Professor Ekaterina Khrameeva

I confirm the absence of any conflict of interest  (Alternatively, Reviewer can formulate a possible conflict)	<b>Date: 07-08-2022</b>
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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

- **Brief evaluation of the thesis quality and overall structure of the dissertation.**  
The thesis presents an excellent work summarizing three studies. The first one covers evolution of adenine-to-inosine mRNA editing in cephalopods. The second one covers evolution of phosphorylated amino acids in mammals. The last one studies hierarchy in clusters of cephalopod mRNA editing sites.
- **The relevance of the topic of dissertation work to its actual content.**  
The topic of the thesis matches its contents well.
- **The relevance of the methods used in the dissertation.**  
Methods used in the thesis are relevant and applied correctly, to my best knowledge, in all three presented studies. The used methods are well described and presented with enough details.

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

The presented research relies on the current state-of-the-art methods and datasets, therefore coping with the international level. Few studies cover mRNA editing, especially from the evolutionary point of view. This thesis fills the missing gap, linking RNA editing and positive selection in cephalopods. In addition, it uncovers the dependence between phosphorylation and selective constraints on local amino acid substitutions – another understudied but important topic.

- **The relevance of the obtained results to applications (if applicable).**

- **The quality of publications.**

High enough to pass the PhD program requirements.

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

The thesis is very well written and I have few comments regarding its content and presentation of the results.

The literature review seems somewhat excessive and though I have enjoyed reading it, I am not sure whether all the presented details are necessary. In several cases, it was difficult for me to trace the relevance of the presented material to the results described in the thesis.

The literature review is followed by three papers, copy-pasted into the thesis as is. Each paper forms a separate chapter (Chapters 3-5) in the thesis, including the paper's abstract, introduction, methods, results, and discussion. In my opinion, it would be better to exclude introductions from these chapters and incorporate them into the literature review instead. Perhaps it would help to tie these three papers together better.

Regarding the presentation of the results, it is not clear what result the Fig. 1B illustrates. It is not discussed in the text. It is hard to see the differences between species because medians are not clearly presented. What conclusion is the reader supposed to make from this figure?

The p-values corresponding to Fig. 2C are a bit confusing:  $p=10^{-22}$  is specified in the panel,  $p=10^{-33}$  is specified in the legend, and  $p<10^{-3}$  is specified in the text. Probably, the differences between them should have been explained better. In Fig. 2D, it would be good to see confidence intervals in some form.

Chapter 3.3.5 is probably more suitable for the Discussion.

In Fig. 7A, it is not clear how the random set of clusters was constructed. I believe the details of the procedure are important to obtain a correct result. Moreover, only two control sets were analyzed. I would suggest to make 1000 control sets here and perform a classical permutation test, to demonstrate that the effect was consistent and significant, and calculate the permutation p-value.

It seems like Fig. 12B and D are missing Y-axes. Or are they the same as in panels A and C? Perhaps thin horizontal lines would help to clarify that.

Why is the Chapter 5.3.3 title highlighted in red?

From Conclusions (Chapter 6), it is not clear how the mRNA editing story is tied together with the

phosphorylation story. It should have been articulated better.

The thesis contains very few typos and grammar issues. I think I've spotted one at page 39, line 4 ("decoding yielding"). Also, there is a missing comma in Fig. 11A legend ("human, mouse and rat"). But what is the meaning of square brackets at page 39 ([neutral]) and page 38 ([function], [usage])?

**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*