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REVIEW

Author: Prof. Dr. Anton Bozhidarov Tonchev, PhD — Head of Department of Anatomy and Cell Biology, Medical University “Prof. Dr. Paraskev Stoyanov” – Varna.

The dissertation for the award of the scientific degree “Doctor of Science” Field of higher education: 4 “Natural Sciences, Mathematics, and Informatics” Professional field: 4.3 “Biological Sciences” Scientific specialty: “Molecular Biology”

Author: Assistant Professor Tihomir Iliev Vachev - Plovdiv University “Paisii Hilendarski”.

Dissertation thesis: “Comparative genomic, transcriptomic and proteomic studies in neurodevelopmental disorders”

1. Subject of review

With an Executive Order № P33-5262 of 29.10.2020 of the Rector of Plovdiv University “Paisii Hilendarski”. I was appointed as a member of the scientific jury to provide a procedure for the protection of dissertation on the topic “Comparative genomic, transcriptomic and proteomic studies in neurodevelopmental disorders” for acquiring the scientific degree ‘doctor of science’ Field of higher education: 4 “Natural Sciences, Mathematics, and Informatics” Professional field: 4.3 “Biological Sciences” Scientific specialty: “Molecular Biology”

The author of the dissertation is Assistant Professor Tihomir Iliev Vachev, PhD from the department of Plant Physiology and Molecular Biology, Faculty of Biology Plovdiv University — “Paisii Hilendarski”.

The set of materials presented in electronic format by Asst. Prof. Tihomir Vachev is in accordance with the Regulations for the development of the academic staff of the University of Plovdiv Article 45 (4) and includes the following documents:

1. Request to the Rector of University of Plovdiv “Paisii Hilendarski” for disclosure of the protection procedure;
2. CV in European format;
3. Notarized copy of the diploma for higher education (Master's degree);
4. Documents from departmental councils, related to reporting of readiness for opening the procedure and preliminary discussion of the dissertation;
5. Dissertation work;
6. Abstract (in English and Bulgarian);
7. List of scientific publications on the topic of the dissertation;
8. Copies of scientific publications;
9. Declaration of originality and authenticity of the attached documents;
10. Reference for covering the minimum national requirements in direction 4.3. Biological sciences. for obtaining the scientific degree "Doctor of Sciences"

The presented documents **cover the requirements of the Law on Development of the Academic Staff in the Republic of Bulgaria and the Regulations of the University of Paisii Hilendarski for admission to the scientific degree “Doctor of Sciences”**.

2. Brief biographical data on dissertant

Tihomir Vachev graduated in Biology from the University of Paisii Hilendarski as a Bachelor, followed by a Master’s degree in Molecular Biology and Biotechnology at the same university. He holds 2 doctoral degrees in “Molecular Biology” at University of Plovdiv “Paisii Hilendarski” and “Medical Genetics” at Medical University – Plovdiv. Head of scientific developments of Bachelors and Masters, graduates, and Ph.D. students at the Department of Plant Physiology and Molecular Biology. A par-

ticipant in 8 national and international scientific projects. Hirsch—index at Google Scholar = 10 (<https://scholar.google.com/citations?hl=en&user=2hyJxMEAAAAJ>). Tihomir Vachev is fluent in written and spoken English.

3. Relevance of the topic and expediency of the set goals and objectives

The emphasis of the research area in the presented dissertation is placed on contemporary molecular genetic issues in neurodevelopmental disorders and in particular ASD and schizophrenia. Neuropsychiatric disorders such as schizophrenia and autism spectrum disorders (ASD) are currently affect millions of individuals around the world and lead to disability and incapacity. The discovery of markers for early diagnosis of these disorders is of particular importance to society, especially as regards markers from accessible sources such as peripheral blood. **Therefore, I appreciate the topic of the dissertation as extremely relevant.** The dissertation presented by Asst. Prof. Vachev aims at conducting Comparative genomic, transcriptomic, and proteomic studies in neurodevelopmental disorders, including ASD and schizophrenia. To achieve this goal, the distant focus on a series of 9 tasks, including classical and new generation sequencing, quantitative PCR, proteome analysis, and subsequent processing of the resulting data through bioinformatics analysis. The purpose and tasks are clearly formulated. **Given the methodologies presented, I appreciate the objective as feasible.**

4. Knowledge of the problem

The introduction clearly motivated the need for research in the field of dissertation. A summary of basic scientific data at the moment on the topic and availability of blank fields, which deserve the original research and analysis of the author. The literary overview, spread over more than 100 standard pages, shows the dissertant's good awareness of available literary sources on the topic of molecular

mechanisms of neurodevelopment disorders. The long list of references in the bibliography itself is indicative of the need to pause with an information avalanche during the work on the dissertation – something that, in my opinion, Asst. Prof. Vachev has successfully achieved.

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5. Study methodology

The inclusion and exclusion criteria for patient selection, methods for the analysis of samples, statistical evaluation of data are clearly presented.

Conclusion: The materials and methods are extremely detailed in a way that would allow the experiments to be repeated by independent researchers.

6. Characterisation and evaluation of the dissertation

The results extend over more than 70 standard pages, illustrated by 58 figures and 15 tables. The figures are of very good quality and clearly visualize the thesis of the dissertation. The results of DNA and RNA sequencing of samples from patients with schizophrenia, ASD, and control groups are consistently presented, followed by

a bioinformatic analysis for differentially expressed genes between control and test groups. The dissertant has detected differentially-expressed microRNAs and protein-coding gene RNAs in peripheral blood. Some of these biomarker candidates have a very interesting expression in the brain (e.g. the FEZ1) gene, which presupposes the development of future developments to examine the expression of candidate genes in tissue and their role in the development of the nervous system.

The discussion is and again demonstrates the good literary awareness and analytical thinking of the dissertant. One's own results are commented in the light of an in-depth synthesis of familiar data in the literature. The introduction of a separate chapter Conclusion supports the summary of results and opens a door to new, future research.

Conclusion: The results presented are of extremely high quality and support the thesis of the dissertation.

7. Contributions and significance of development for science and practice

As the main contributions of the dissertation, I appreciate the identification of micro RNA and RNA of protein-coding genes with potential biomarker characteristics in RAS. I accept the scientific and methodological contributions defined by the dissertant, including the application of the technologies "Whole-Exome Sequencing", "RNA-Sequencing" and "Small RNA-Sequencing" in Bulgaria.

Conclusion: I confirm that the contributions are sufficient for the acquisition of the scientific degree "Doctor of Sciences".

8. Assessment of the publications on the dissertation

The list of publications annexed to the procedure for acquiring the scientific degree "Doctor of Sciences" includes 9 publications in Bulgarian and international

journals. The quartiles of the publications are reported respectively the metric of the scientific editions referred to in Scopus SCImago Journal Rank (SJR) <https://www.scimagojr.com/journalrank.php>.

Four of Asst. Prof. Vachev's publications are in journals with impact factors. According to the indications for grouping of scientific journals in each scientific field, namely, the four quartiles (quarters). Asst. Prof. Vachev's publications are as follows. Two of the publications are with Q2, four with Q3, and two with Q4. One of the journals (Biodiscovery) in which the dissertation has a publication does not have a quartile but due to its connection with the topic of the dissertation the publication is presented in the list of publications. The applicant meets the minimum required points by a group of indicators for the degree of Doctor of Science – of the required 350 points according to the indicators A, B, D, E – the candidate has 436 points. A list of publications with their respective citations annexed to the procedure for acquiring the scientific degree “doctor of science” shows 56 citations.

9. Personal participation of the author

Based on the submitted dissertation and publications, I believe that the personal involvement of the dissertant in the conducted study is central and that the formulated contributions and results obtained are **the personal merit of** Asst. Prof. Tihomir Vachev. For all of this, I refer to the fact that in all of these publications related to the dissertation the dissertant is a leading author.

10. Summary

The presented summaries in Bulgarian and English present the most important results of the study. Summaries have been prepared in accordance with the relevant requirements of the Law for development of the academic staff in the Republic of

Bulgaria (ZRASRB). The Regulations for application of ZRASRB and the respective Regulations of Plovdiv University "Paisii Hilendarski".

11. Critical remarks and recommendations

It would be good to extend the study by increasing the number of cases studied.

12. Personal impressions

Asst. Prof. Tihomir Vachev is a molecular biologist with diverse interests and competencies in the field of biomedicine. It has the necessary potential for participation in interdisciplinary research and interaction with specialists from biomedical specialties for formulating and solving scientific tasks concerning each medical field, with a focus on neuropsychiatric disorders. I believe that the dissertation presented is only a step in Asst. Prof. Vachev's future successful career.

13. Recommendations for future use of dissertation contributions and results

I recommend that the identified micro RNA and expressed genes, whose levels have been altered by ASD or schizophrenia, be compared to the available databases for the cells in the central nervous system derived from RNA sequencing of single brain cells.

CONCLUSION

The dissertation of Asst. Prof Tihomir Iliev Vachev, PhD from the Department of Plant Physiology and Molecular Biology, Faculty of Biology of Plovdiv University "Paisii Hilendarski" is dedicated to an extremely relevant problem. The Dissertant has presented a number of original results, produced as a result of the application of clinical, genetic, and bioinformatics methods, which the author skillfully uses to

solve the set tasks. The dissertation is highly interdisciplinary and includes original scientific data from at least several areas of biomedicine, including genetics, molecular biology, psychiatry, neurosciences. I believe that the dissertation is fully in line with the requirements of the Law for the development of the academic staff in the Republic of Bulgaria. The Regulations for application of the Law and the respective Regulations of Plovdiv University "Paisii Hilendarski". That is why I will vote positively and allow myself to recommend the same to the other members of the esteemed Scientific Jury, determined by Order № P33-5262 of 29.10.2020 of the Rector of Plovdiv University "Paisii Hilendarski".

Reviewer:

Prof. Dr. Anton B. Tonchev, MD, DSc
Department of Anatomy and Cellular Biology
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Varna, 01.02.2021