Review Report on PhD Thesis

The doctoral thesis titled "Mouse models for Angelman syndrome: generation and characterization" by author Linn Amanda Syding summarizes the results of her scientific work at the Dept. of Transgenic Models of Diseases; Institute of Molecular Genetics AS CR.

The thesis has an adequate form and content. The work is structured in the commonly used way of writing doctoral thesis, *i.e.* abstract, theoretical introduction, aims of the work, followed by material and methods, results, appropriately structured discussion, summary, references and an overview of the author's publications. In terms of language, the text is well-written with a minimum of typos.

The aim of the thesis is to create and study the novel animal models of Angelman syndrome (AS). Angelman syndrome is a rare hereditary neurodevelopmental disease with complex clinical manifestations. Typically, it causes delayed development, problems with intellectual disability, and sometimes, seizures. Patients suffering from AS often smile and laugh frequently. The symptoms generally become noticeable and diagnosable by one year of age. People with AS tend to live close to a normal life span, but the disorder can't be cured. AS forms the remarkable and interesting pair of diseases with Prader-Willi syndrome. The diseases are due to a lack of function of part of chromosome 15. Most of the time, it is due to a deletion or mutation of the UBE3A gene on that chromosome. What makes this field really scientifically exciting is not the medical relevance only, but above all the phenomenon of genomic imprinting. Where, depending on which the chromosome (from the mother or the father) is imprinted, one or the second disease will develop. It is noteworthy that both diseases have different symptoms. The author correctly mentioned all these biological aspects in the introduction and put her results into the context of the current state of knowledge in this area.

The author's intention is to use the newly created models to understand the role of the Ube3a and Gabra5 genes in biology of AS. The intention is to gain more knowledge about the possible use of these two genes for future therapeutic interventions in AS.

All in all, the PhD candidate succeeded in achieving the objectives and aims of the doctoral thesis. At the same time, it is obvious that the achieved results offer an opportunity for continuing further and deeper research.

Questions:
- AS is a neurodevelopmental disease showing symptoms already in early childhood. How does motor and cognitive development occur in pups between PD9 and PD45?
- Genomic imprinting is different in humans and mice during embryonic development. Some studies report that in AS, the genes are functional during fetal development. Could you describe the functionality of the studied genes during early development in your models?
- The conclusion of Aim 3 show the functional compensation of Gabra5 because of a constitutive deletion of the gene. However, it is not shown in which development period the compensation could occur. Could you discuss at what developmental period in these neurodevelopmental disease models compensation might have occurred?

- Conclusion:

It is obvious that the author demonstrates creative activity, the ability to study scientific literature, plan and conduct scientific experiments. She successfully presented the results in scientific literature. These publications in journals with IF, forming the basis of the doctoral thesis, meet the requirements given by the rules of Faculty of Science Charles University

In conclusion, the doctoral thesis clearly demonstrates that PhD candidate has all the prerequisites for an independent creative scientific work. The reviewed thesis fulfill all requirements posed on doctoral thesis aimed for obtaining PhD degree. Therefore, I recommend the thesis for the defense and award of the title "Ph.D."

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