**Examiner’s Report**

**Student:** Qinyuan Yu

**Dissertation / Research Project:** Role of Altered Cerebral Proteolysis in the Pathogenesis of Sporadic Alzheimer's Disease

**Recommended grade:**

Please indicate % mark in the relevant box below. Grade level descriptors are provided at the end of this document to assist you in determining an appropriate grade.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Class of Honours** | 1st | | | 2nd div I | 2nd div II | | None | | | Fail |
| Grade | A+ | A | A- | B+ | B | B- | C+ | C | C- | D |
| GPA | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | 0 |
| % mark range | 100-90 | 89-85 | 84-80 | 79-75 | 74-70 | 69-65 | 64-60 | 59-55 | 54-50 | <50 |
| **Recommended % mark** |  |  |  |  |  | X |  |  |  |  |

**Please comment on the dissertation under the following headings:**

*Introduction & statement of problem*

The English is excellent, but I feel:

\* The introduction is very long and detailed, and almost constitutes a review of Alzheimers from scratch. Is this necessary? In the end it comes down to Alzheimers-is-bad and we-don't-know-the-cause. That is sufficient to motivate the research. So the effort in the introduction should be aimed at explaining why the specific approach you are taking -- measuring proteases etc -- is relevant and useful.

Only in the last paragraph do you get to urea being 6 times higher as a result of protein breakdown.

What would be nice would be to see discussion of questions like:

\* Is protease dysregulation likely to be a cause of AD, or a downstream effect? I'm no expert in this area, but it is imaginable that tissue and cell damage and death, in general, causes the release of proteases and/or upregulation of them in immune cells. It is interesting to study either way, but it seems like a significant question, if the motivation is the mechanism of disease!

*Methodology & mastery of techniques*

It appears that this thesis will be the bioinformatics step of a larger project, and aims to measure the difference in protease and protease inhibitor express in AD case and control brains.

It is fine for a Masters thesis to just focus on one aspect of a larger project, but given the bioinformatics focus, I would have hoped to see:

* Some discussion of the computational tools to be used
* Some discussion of the present state of the data. Is it raw outputs from mass specs etc., or some more processed output? I assume the latter. The Methods mention “Use the database to identify proteases and protease inhibitors present in control human brains,” several times, but this comes out of the blue, with no discussion of what this database is, or what is contained in it. I assume it is basically the “relative protease and protease-inhibitor expression data” derived from ITRAQ experiments, mentioned earlier.
* From there, I guess the method is to
  + List the proteases/inhibitors found in each brain region
  + Look for differences in expression between cases & controls
  + Look for the same, but at a pathway level
  + Look for key proteases in these pathways (I assume these are proteases that activate other proteases, or something like that)
  + Measure the differences by brain region with “Bayesian modelling”
* Bayesian modelling is repeatedly mentioned, but with no detail of how this works or what models are used. I am sure the advisor, Prof. Cooper, is experienced in this area and guide the student, and probably the methods are off-the-shelf rather than something the student has to design from scratch, but ideally the proposal would discuss this aspect. I imagine that the point of using Bayesian modeling instead of standard frequentist summary statistics is to deal appropriately with issues like:
  + small sample size
  + unusual distributions (e.g. relative abundances)
  + detection biases etc. from the iTRAQ technique

…it would be nice to see these discussed!

Results, data treatment & analysis

N/A, except that the samples & data have already been collected & stored etc.

Discussions & conclusions

Brief, but does mention some limtations of the techniques and sample size.

Organisation & presentation

This was good as far as it went.

Originality

The proposal was mostly a general overview of dementia generally and Alzheimer’s specifically. While it demonstrates good writing and mastery of the general topic, unfortunately there was far too little on the details of specific research being done. Ideally a proposal would quickly drill down to the specifics of the research & not spend too much time on generic background.

This would also give the student a chance to express originality in terms of exactly how to go about the work; however, much of the creativity comes during the research, not before it.

Other comments (supervisor should comment here on degree of assistance required to complete experiments/produce the dissertation)

Overall opinion:

Upsides:

Detailed & well-written overview of Alzheimers & the literature’s challenges in identifying mechanism

Decent questions, understanding of the source data

Flawless English

Downsides:

Little or no critical discussion of a key issue, i.e. whether protease differences would be a cause, effect, or both of Alzheimers / tissue & cell damage

Little detail about the details of the bioinformatics / Bayesian modeling involved. Does this require programming in a language like R? A specific software package that does the Bayesian modelling? Why use Bayesian over frequentist methods, and what models specifically are useful here?

I think the review, judged as a review, is an A, and the description of the methods done by the group before this students’ involvement is good as well. But the description of the details of the student’s actual planned work is very weak, maybe C-. Since the downsides are the most significant points for the planned research, but I think probably it will go OK with guidance as the student is obviously good at learning material, I give it a B-.

Minor points:

Italicize journal names

I’d use “sex” rather than “gender” of sampled individuals, as we are talking biology here.

Name of examiner: \_\_Dr. Nick Matzke\_\_ Signature: \_\_ \_\_\_

**POSTGRADUATE DISSERTATIONS AND PROJECTS**

**MARKING GUIDELINES**

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| **Grade** | **Short comment** | **Explanation** | **Description** |
| A+ 90-100% | Exceptionally high level of performance | Fulfils all descriptors to an unusually high standard | * Well-structured and integrated research plan; * Well formulated research questions and appropriate investigative methodology used; * Excellent knowledge and understanding of subject; * Excellent knowledge of the literature and critical evaluation of previous work; * Significant new technical skills mastered * Appropriate data collected (if applicable) and rigorous and critical data analysis; * Clear understanding of significance of the data/evidence; * High level of critical thinking; * Arguments presented logically and coherently; * Conclusions comprehensive and well-justified; * Research project/dissertation well-constructed and appropriately illustrated. |
| A 85-89% | Clear high quality performance | Fulfils all descriptors to a high standard |
| A- | First class | Fulfils all descriptors to a high standard but not consistently |
| 80-84% |  |
| B+ | Very good | Fulfils all descriptors to a high standard by not consistently | * Sound research plan; * Good formulation of research questions and appropriate investigative methodology used; * Good grasp of subject matter; * Good knowledge of the literature and evaluation of previous work; * Appropriate data collected (if applicable) and good data analysis; * Some appreciation of the significance of the data/evidence; * Evidence of critical thinking; * Arguments presented reasonably well; * Some sound conclusions drawn; * Research project/dissertation reasonably well constructed and illustrated |
| 75-79% |  |
| B | Good | Fulfils most descriptors to a good standard |
| 70-74% |  |
| B- | Competent | Fulfils most descriptors to a good standard, but not consistently |
| 65-69% |  |
| C+ | Clear pass | Fulfils most descriptors to a competent standard | * Reasonable research plan outlined; * Research questions formulated and adequate research methodology applied; * Knowledge of subject matter shown but with some lapses, inadequacies and errors; * Adequate attempt at data analysis (if applicable) but may lack adequate justification; * Originality and critical thinking present but limited; * Arguments supported by some evidence; * Research project/dissertation adequately presented |
| 60-64% |  |
| C | Pass | Fulfils most descriptors to a competent standard but not consistently |
| 55-59% |  |
| C- | Marginal pass | Fulfils some descriptors to an adequate standard |
| 50-54% |  |
| D | Fail | Fails to fulfil enough descriptors to a competent standard | * Work lacks breadth and depth; |
| <50% |  | * Understanding and coverage inadequate; * No attempt at interpretation; |
|  |  | * Research project/dissertation poorly presented |