

Thesis Changes Log

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PhD Program: Life Sciences

Title of Thesis: Molecular Signatures and Mechanisms behind Lifespan Extensions

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The thesis document includes the following changes in answer to the external review process.

Reviewer Comment 1) Results of PCA analysis are described, but a figure would be useful (p. 45).

Author: Figure was included (p. 46, top).

Reviewer Comment 2) In fig. 6A, no scale is given in the right panel: even if it is the same as in the left one, it would be useful.

Author: Scale was added (p. 49).

Reviewer Comment 3) Student's t-test was applied, but it is not clear whether the distribution had been tested for normality (p. 64)

Author: Statistical significance was re-estimated using Mann-Whitney U test (corrected at p. 65).

Reviewer Comment 4) Does the observation that decreasing-methylation sites are initially hypermethylated and increasing-methylation sites are initially undermethylated (pp. 71-72) mean that the variance of methylation (over all changing sites or even over all sites) decreases with age? – to some extent this is demonstrated using Shannon's entropy in 3.2.4, but a direct test also might be relevant.

Author: It is interesting question. Methylation fraction follows bimodal distribution (fig. 14, p. 80) with pretty narrow peaks on extremes (near 0 and 1). With age these peaks get 'relaxed' (entropy increases), and within them variance increases with age. On the other hand, in general, methylation fraction moves towards center. This is clearly seen on fig. 14, which gives complete picture of age-related changes of methylation fraction.

Reviewer Comment 5) The last para in p. 20 deals with gene expression associations with maximum lifespan, but the positive selection discussed here has affected gene sequence, not expression.

Author: Positive selection at gene sequence level was mentioned as an additional argument supporting the association between DNA repair system and longevity across species. Sentence was rephrased to make it clearer (p. 20).

Reviewer Comment 6) The last phrase in p. 21 states that a “2-fold decrease in mutation rate may result in 100-fold increase in cell mass free from cancer”; this is formally correct (yes, it MAY result in such an increase), but it is not explained how these figures were obtained, and no reference is provided.

Author: These numbers were obtained based on mathematical modelling of cancer incidence. Explanation and corresponding reference were added (p. 21-22).

Reviewer Comment 7) I don't see why the deficit of the signal of apoptosis in NMR implies higher senescence in this species (p. 51, top).

Author: It doesn't imply higher absolute level of senescence. Relative preference of senescence over apoptosis by NMR cells was meant. Sentence was rephrased to make it clearer (p. 51).