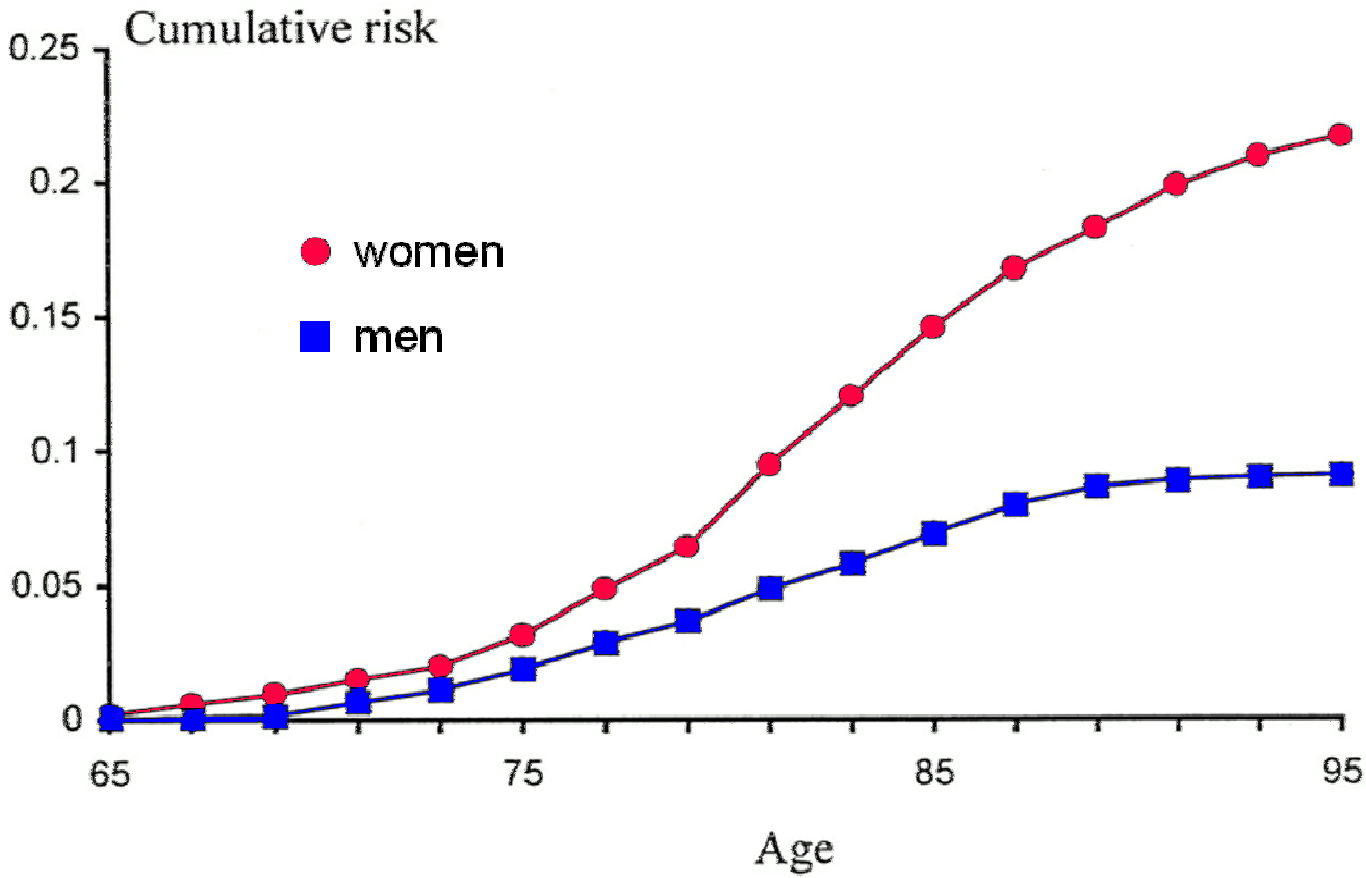
Modelling gender-specific regulation of tau in Alzheimer's disease

Motivation: Age-dependence of gender-differences in AD

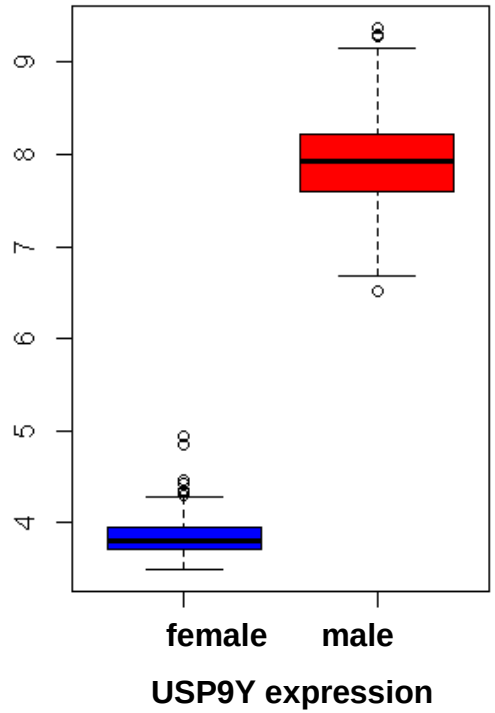
Sex-specific cumulative risk for a 65-year-old to develop AD by 95 years of age.

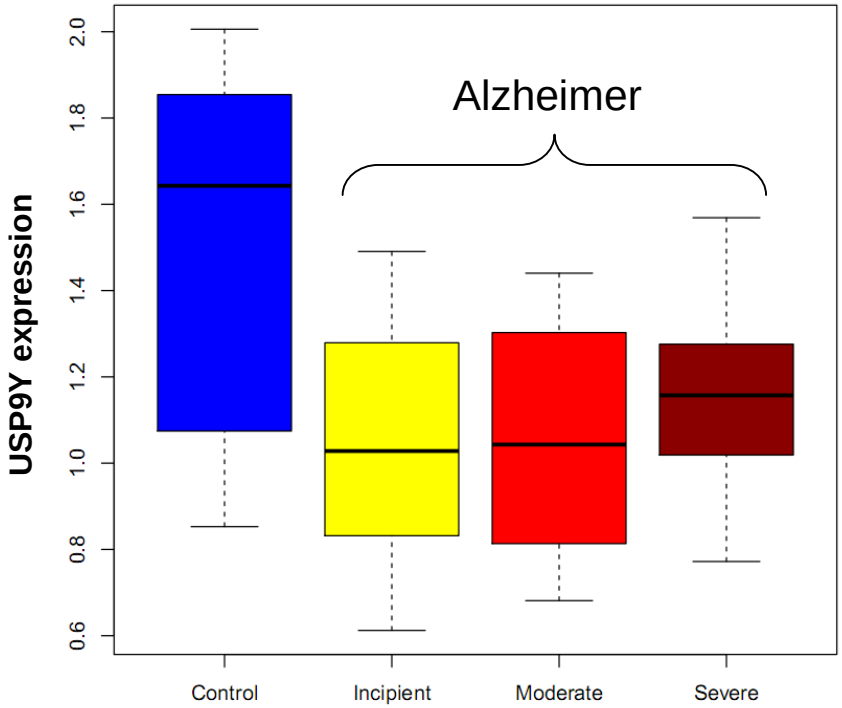


Adapted from Andersen K et al. Neurology 1999;53:1992-1992

→ significant difference also after adjusting for differential survival

Candidate gene USP9 – Gene expression data analysis

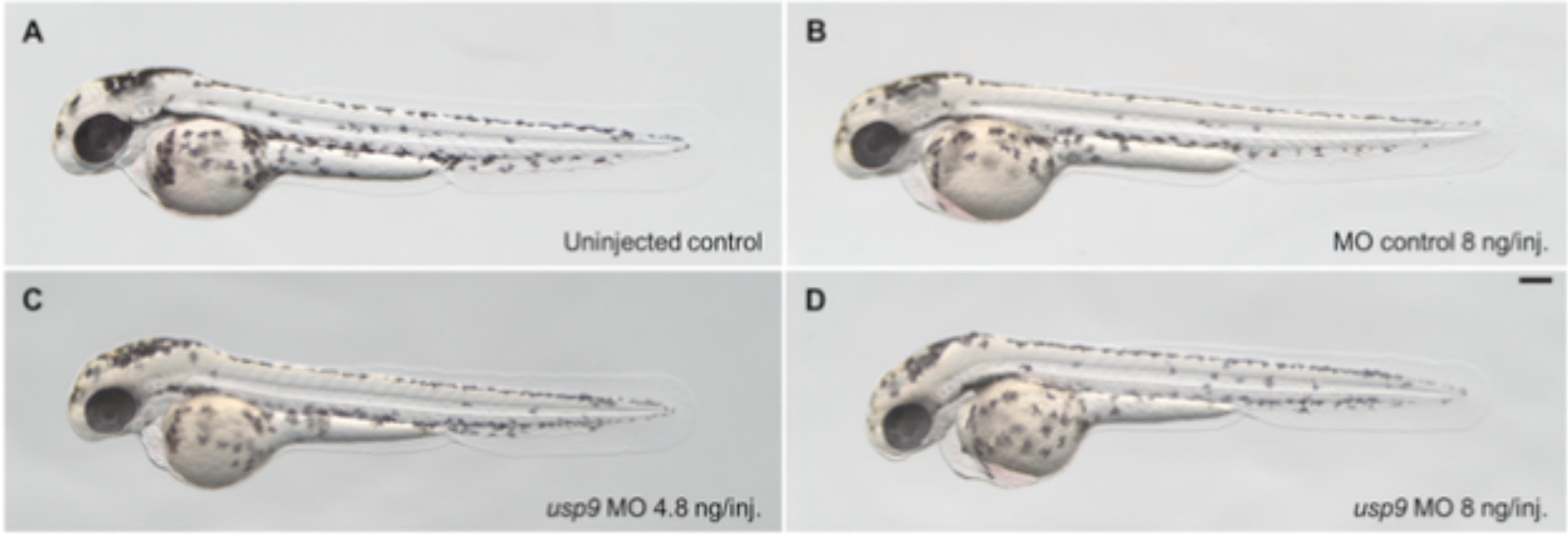




Left: USP9Y is one of the genes with the largest gender differences in gene expression across multiple brain regions (USP9Y difference is not compensated by USP9X, dataset by Kang et al., 2011).

Right: USP9Y down-regulation in human post-mortem hippocampus samples for incipient, moderate and severe cases of Alzheimer's disease as compared to non-demented controls (dataset by Blalock et al., 2011)

Analysis in zebrafish embryo model (USP9 Knockdown)



A: Zebrafish prior to injection of morpholino oligos (MO) for *usp9* knockdown

B: 8 ng control injection

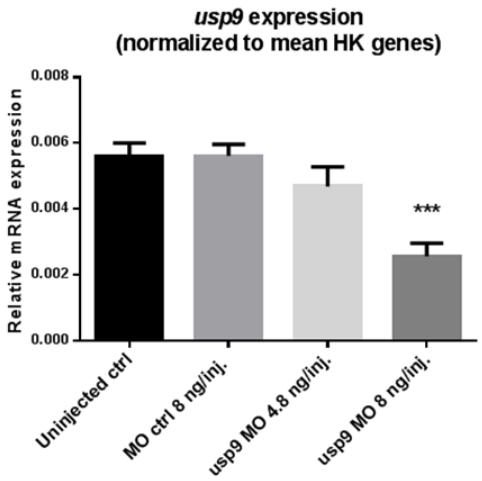
C: 4.8 ng MO injection

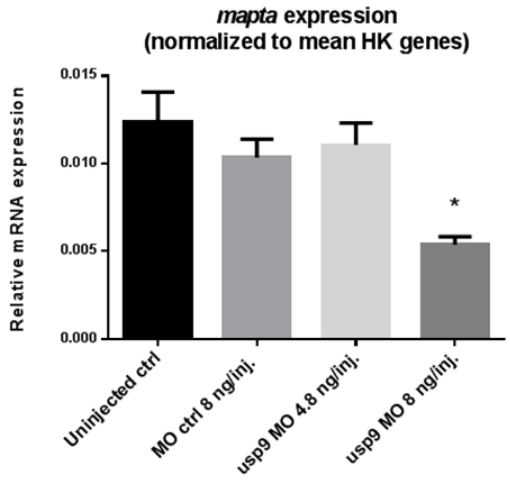
D: 8 ng MO injection

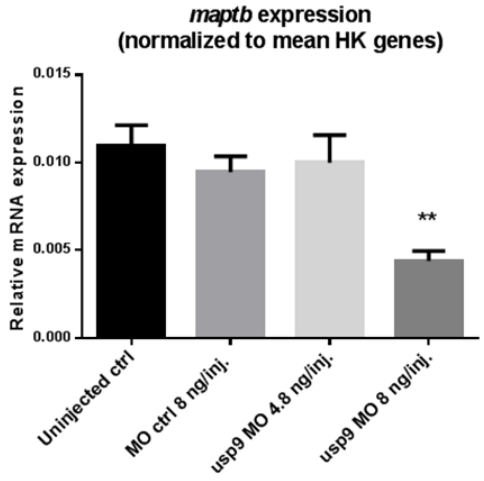
Analysis of usp9/tau associations in zebrafish

- Zebrafish have 2 MAPT-paralogs, *mapta* & *maptb*, which resemble the two tau isoforms in humans → Analyze *usp9* knockdown effect on *mapta* & *maptb*

- The morpholino knockdown of *usp9* results in a concentration-dependent decrease of *mapta* and *maptb* gene expression

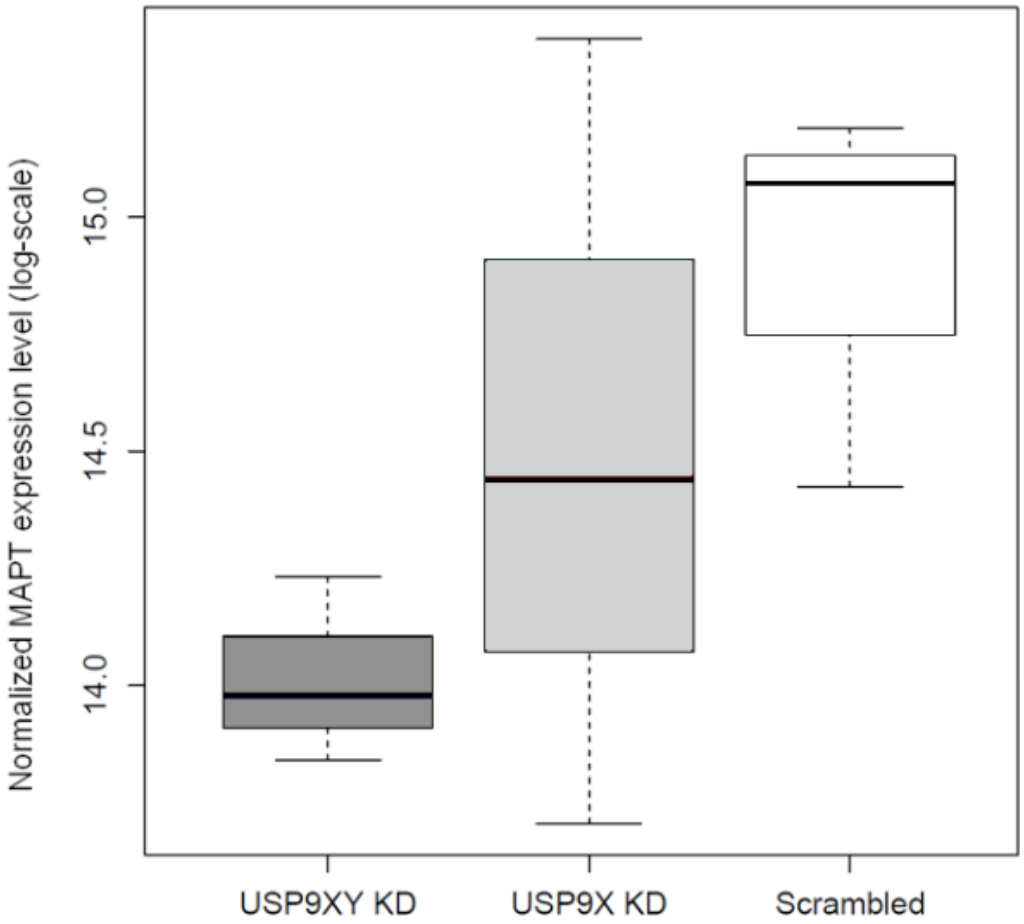




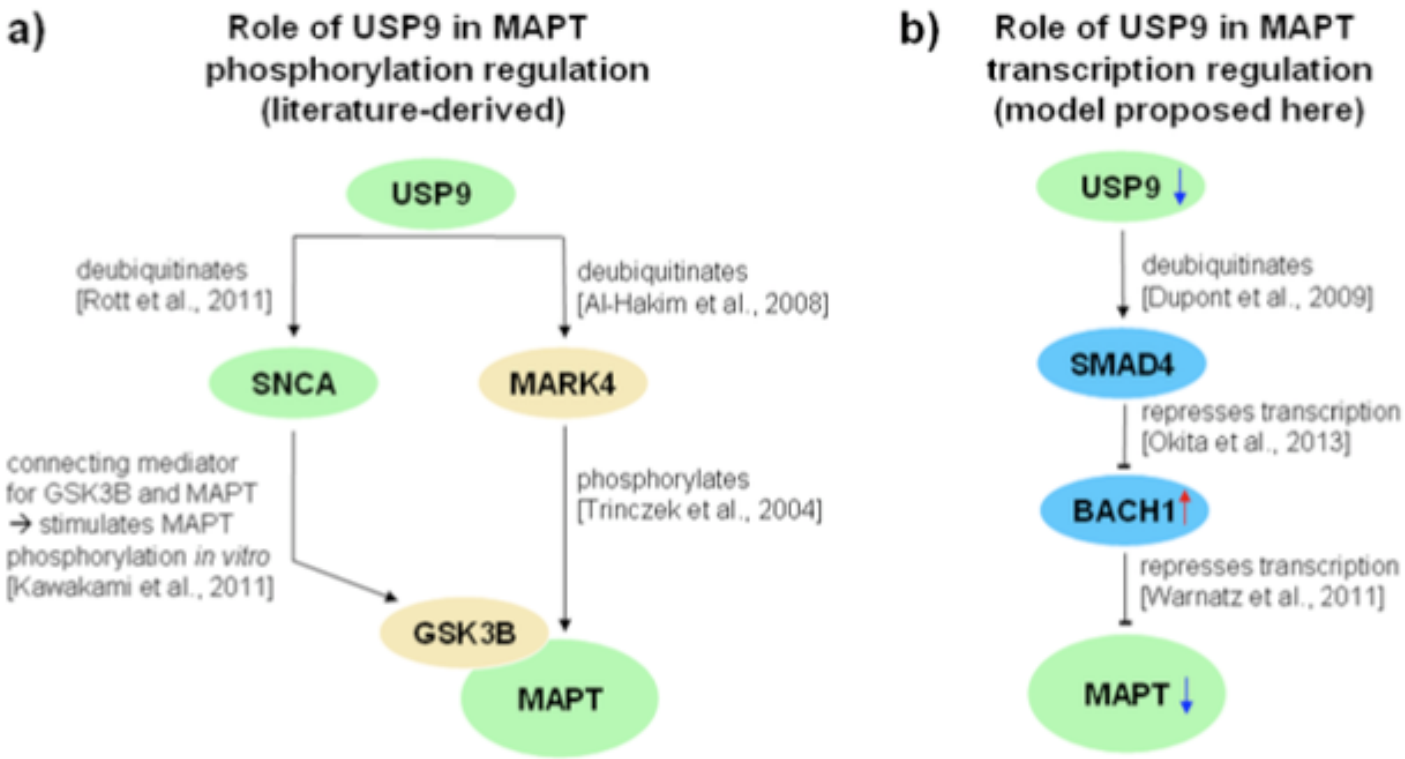


Analysis of USP9/tau associations in a cell culture model

- Knockdown of USP9X/Y and USP9X results in significantly reduced MAPT concentration levels
- The effect is strongest for the combined knockdown of USP9X and USP9Y
- High correlation of gene expression fold changes in USP9X/Y und USP9X knockdowns ($r = 0.965$, $p < 2.2E\text{-}16$ for the top 1000 most significantly altered genes) → suggests similar functions of the two USP9 variants



Model for the role of USP9 in MAPT regulation



a) USP9 can modulate MAPT phosphorylation via SNCA and MARK4

b) USP9 can modulate MAPT gene expression via SMAD4 and BACH1

Summary

Overview of findings

- Significant alterations observed in USP9 and MAPT gene expression in Alzheimer patients (*post mortem* brain samples) as compared to unaffected controls

- Association between USP9 knockdown und alterations in MAPT gene expression in both zebrafish and cell culture model experiments (+ significant correlation in human *post mortem* brain samples)

- New USP9/MAPT regulation model is consistent with measured experimental data and regulatory information from the literature

References

1. S. Köglsberger, M. L. Cordero-Maldonado, P. Antony, J. I. Forster, P. Garcia, M. Buttini, A. Crawford, E. Glaab, Gender-specific expression of ubiquitin-specific peptidase 9 modulates tau expression and phosphorylation: possible implications for tauopathies, Molecular Neurobiology (2016), in press (doi: 10.1007/s12035-016-0299-z)
2. E. Glaab, R. Schneider, *RepExplore: Addressing technical replicate variance in proteomics and metabolomics data analysis*, Bioinformatics (2015), 31(13), pp. 2235
3. E. Glaab, *Using prior knowledge from cellular pathways and molecular networks for diagnostic specimen classification*, Briefings in Bioinformatics (2015), 17(3), pp. 440
4. E. Glaab, R. Schneider, *Comparative pathway and network analysis of brain transcriptome changes during adult aging and in Parkinson's disease*, Neurobiology of Disease (2015), 74, 1-13
5. N. Vlassis, E. Glaab, *GenePEN: analysis of network activity alterations in complex diseases via the pairwise elastic net*, Statistical Applications in Genetics and Molecular Biology (2015), 14(2), pp. 221
6. E. Glaab, *Building a virtual ligand screening pipeline using free software: a survey*, Briefings in Bioinformatics (2015), 17(2), pp. 352
7. E. Glaab, A. Baudot, N. Krasnogor, R. Schneider, A. Valencia. *EnrichNet: network-based gene set enrichment analysis*, Bioinformatics, 28(18):i451-i457, 2012
8. E. Glaab, R. Schneider, *PathVar: analysis of gene and protein expression variance in cellular pathways using microarray data*, Bioinformatics, 28(3):446-447, 2012
9. E. Glaab, J. Bacardit, J. M. Garibaldi, N. Krasnogor, *Using rule-based machine learning for candidate disease gene prioritization and sample classification of cancer gene expression data*, PLoS ONE, 7(7):e39932, 2012
10. E. Glaab, A. Baudot, N. Krasnogor, A. Valencia. *TopoGSA: network topological gene set analysis*, Bioinformatics, 26(9):1271-1272, 2010
11. E. Glaab, A. Baudot, N. Krasnogor, A. Valencia. *Extending pathways and processes using molecular interaction networks to analyse cancer genome data*, BMC Bioinformatics, 11(1):597, 2010
12. H. O. Habashy, D. G. Powe, E. Glaab, N. Krasnogor, J. M. Garibaldi, E. A. Rakha, G. Ball, A. R Green, C. Caldas, I. O. Ellis, *RERG (Ras-related and oestrogen-regulated growth-inhibitor) expression in breast cancer: A marker of ER-positive luminal-like subtype*, Breast Cancer Research and Treatment, 128(2):315-326, 2011
13. E. Glaab, J. M. Garibaldi and N. Krasnogor. *ArrayMining: a modular web-application for microarray analysis combining ensemble and consensus methods with cross-study normalization*, BMC Bioinformatics,10:358, 2009
14. E. Glaab, J. M. Garibaldi, N. Krasnogor. *Learning pathway-based decision rules to classify microarray cancer samples*, German Conference on Bioinformatics 2010, Lecture Notes in Informatics (LNI), 173, 123-134
15. E. Glaab, J. M. Garibaldi and N. Krasnogor. *VRMLGen: An R-package for 3D Data Visualization on the Web*, Journal of Statistical Software, 36(8),1-18, 2010