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MIND THE DATA

Search for Gender Based Differences In Alzheimer's Disease

Round II: 21CBT INNOVATION AWARD FINALIST

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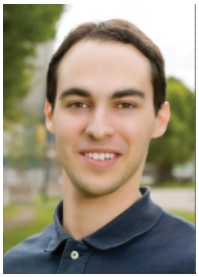

Enrico Glaab, PhD

AGE-RELATED GENDER DIFFERENCES IN BRAIN EXPRESSION LEVELS OF TAU-INTERACTING UBIQUITIN-SPECIFIC PEPTIDASE 9 AND POSSIBLE IMPLICATIONS FOR ALZHEIMER'S DISEASE

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Recent studies on aging of the human brain show that age-related gene expression changes may display significant differences between the genders. One of the genes with the largest differences between male and female expression levels across multiple brain regions during adulthood is the Y-chromosomal ubiquitin-specific peptidase 9 (USP9Y; the differences are not compensated by the female homologue USP9X). Interestingly, in *post-mortem* brain samples from male Alzheimer's disease (AD) patients, a significant down-regulation of USP9Y is observed as compared to unaffected male controls, while no significant changes are detected for USP9X. Studying the protein interaction network reveals associations of USP9Y with microtubule-associated protein tau (MAPT), known for the formation of neurofibrillary tangles in AD and with SIRT1, previously linked with aging/longevity and AD. USP9X/Y is also a known regulator of the TGF-beta/BMP signaling pathway and deubiquitinates monoubiquitinated SMAD4, opposing the inhibitory activity of E3 ubiquitin-protein ligase TRIM33 and resulting in downstream TGF-beta activation. Since previous studies showed neuroprotective effects for TGF-beta activation in multiple *in-vitro* and *in-vivo* models of neurodegeneration, and fly AD models affirm an involvement of USP9X/Y in MAPT regulation, the combined observations suggest that age-dependent higher USP9X/Y levels in males may contribute to previously observed gender differences in AD.

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