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Interactions Between Autophagy, Herpesvirus and Neurodegeneration in Alzheimer’s Disease

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Introduction

Since the 1960s viral pathogenesis researchers have considered herpesviruses as an underlying factor for Alzheimer’s disease (AD). We reported molecular interactions between herpes simplex virus type 1 (HSV-1) and the amyloid precursor protein, the parent of amyloid plaques pathognomonic for AD (Sapate-Krishnan et al 2003, Chen et al 2011). Furthermore, several studies report biochemical interactions between HSV-1 and autophagy. Using several brain banks for specimens of four brain regions in post-mortem of individuals with and without cognitive impairment prior to death, Readhead et al. 2018 found molecular-genetic evidence linking activity of 6 different human herpesviruses to AD, including HSV-1, HSV-2, HHHN, HHHN', UUV and CMV. Of these, HHHN, a common virus causing milder childhood illness and though to be a nuisance, came out as most significant. Using a QTL approach, a network of candidate AD-associated genes were found that correlated with viral load and autophagy.

Hypothesis

Investigate the role of autophagy related genes in Alzheimer’s Disease (AD).

Finally we search for QTLs that have correlations with three parameters: Viral Load, Viral Activity and AD features.

Methods and Goals: Mine QTL for ATG

Method:

Computational analysis of host QTL associated with viral activity, clinical dementia ratio, amyloid deposits and Braak stage Goals:

- To establish a computational processing environment for parsing relationships between viral and host QTL, Alzheimer’s disease (AD) and autophagy.
- To determine which genes identified as QTL correlate with cognitive impairment and AD histopathology.
- So far, we found several autophagy-associated genes among the host QTL segregating with virus.
- We are developing MATLAB script to mine the QTL data more extensively for the ATG discovered in our ML approach.

Conclusion

- eQTL includes multiple autophagy-associated gene
- These sites correlate with AD risk
- Herpesvirus influence regulation of autophagy-associated genes

Future Directions

- Validate these findings with labs experiments, similar to our previous work with APP (Cheng et al 2011 and Bealer and Wu, 2019): siRNA knockdown, measure viral production and protein expression.
- Develop and apply machine learning (AI) to any other hidden correlations that we may have missed.
- Use machine learning and historical information of patients to accurately predict occurrence of AD based on viral infections.
- Treat those with predicted AD with antivirals early.

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