J Neurol Disord 2015, 3:3
http://dx.doi.org/10.4172/2329-6895.S1.003

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International Congress on
Neuroimmunology and Therapeutics
DoubleTree by Hilton Hotel San Francisco Airport, San Francisco, CA, USA

Parallel mRNA and miRNA analysis shed light on the first genomic overlaps between HIV-associated dementia (HAD) and Alzheimer's disease

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Background: HIV-1 infection is the commonest cause of HIV-1-associated dementia (HAD) in adults <40 years of age and is an important issue in neuropsychiatry. As HIV-infected patients live longer, chronic diseases typical of aging, such as Alzheimer's disease (AD) and Parkinson's disease (PD), are becoming common. Some patients with HIV dementia also develop Alzheimer's disease (AD) and Parkinsonism bearing few anatomical, clinical and proteomic similarities. Therefore, the main objective of the work was to delineate correlations between gene expression (mRNA) and gene regulation (miRNA) to facilitate the understanding of genomic overlaps shared between pathogenesis of these dementing viral and non-viral neurodegenerative disorders. We aimed to delineate genomic overlaps between HAD and Alzheimer's disease by focusing into Alzheimer's disease pathway using quantitative gene expression and complimented by genome-wide microRNA (miRNA) unveil how the gene expression and is regulation by miRNA in viral and non-viral neurodegenerative diseases.

Methods: We studied age-matched HIV+HAD, HIV+ non-HAD, Alzheimer's disease and double negative control brains. RT2 Profiler PCR array focused in Alzheimer's disease pathway was used for quantitative mRNA expression, complimented by genome wide Affymetrix miRNA (V1.0) analysis to define regulation of gene expression. Target scan was used for defining global gene targets and the AD pathway-specific target genes for each DE miRNA. Bioinformatic analysis was done in Genespring and SA Biosciences online tools. Data validation was done using miRNA Q-PCR and Western blot analysis.

Results: The HIV-infected brains showed considerable genomic overlaps with the genes in the AD pathway, which were uniquely enriched in HIV-AD (31 of 84 genes, 42%) followed by the HAD group (28 of 84 genes, 33%), which were characterized by high-fold expression changes in SERPINA3, CASP4, APP, GNB1 and SNCA genes also evident from a multi-group analysis. Interestingly, the SERPINA3 gene 45 and 19-fold up-regulation in HIV-AD and HAD patients, but showed low expression in HIV-ND and AD patients, suggesting the SERPINA3 gene expression was regulated by the expression of actively replicating HIV. Further, the unique identification of miRNA-19a overlapping between HAD and AD showed that it could target 13 of 84 genes in the AD pathway and 7 of these 13 genes were involved in beta amyloid generation, further suggesting the possible role of miRNA-19a in the regulation of genes involved in neurodegenerative process and its overlap between viral and non-viral neurodegenerative diseases is functionally vital. This further suggests intrinsic functional relationship between mRNA and miRNA.

Conclusions: This is the first evidence demonstrating considerable genomic overlaps between viral and non-viral neurodegenerative disease demonstrating intrinsic functional relationship between mRNA and miRNA. Overlapping miRNA-19a, which predominantly targets genes in neurodegenerative pathways, may be involved in the regulation of this process in both HIV-infected and AD individuals. This may provide further insights for the development of new generation of biomarkers for AD and possible other forms of dementias afflicting man.

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