THE FUNCTIONAL ROLE OF MICRORNA TARGET SITE POLYMORPHISMS IN THE 3’UTRS OF BACE1 AND APP

C. Delay1,2, S.S. Hébert1,2

1Laval University, 2CRCHUQ, Axe Neurosciences, Quebec, QC, Canada

Introduction: It is becoming increasingly acknowledged that polymorphisms in microRNA (miRNA) target sites (PolymiRTS) may influence neurological disorders, including Parkinson's disease and frontotemporal dementia. A number of PolymiRTS in the 3’ untranslated region (3’UTR) of APP and BACE1 genes have recently been identified, some of which are found exclusively in patients suffering from Alzheimer’s disease (AD).

Aims: Most complex diseases are caused by a combination of genetic risk variants. Given recent findings, we hypothesize that PolymiRTS could contribute significantly to risk for AD by affecting miRNA binding and increasing the expression of genes like APP and BACE1 involved in the amyloid cascade.

Methods: Using various bioinformatics logarithms, we established a detailed list of potential miRNA binding sites in the 3’UTRs of APP and BACE1. The corresponding miRNAs were tested through luciferase reporter assays as well as by Western blotting for their potential to alter APP and BACE1 expression. In order to further establish whether polymorphisms in the 3’UTR of APP and BACE1 affect the function of the identified miRNAs, mutagenesis of the 3’UTR of these genes and subsequent luciferase reporter assays were performed.

Results: We have identified novel miRNAs that regulate BACE1 and APP expression. Our results suggest that certain polymorphisms influence miRNA binding and therefore expression.

Conclusions: These data could help to focus future association studies aimed at identifying novel risk factors for AD. The identification of novel miRNAs involved in the physiological regulation of APP and BACE1 may provide novel targets for potential future diagnostics and therapy purposes.