# Post-transcriptional Gene Silencing in Neuronal Differentiation, Development and Schizophrenia

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## DECLARATION

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**NATALIE J. BEVERIDGE** **March, 2011**

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## ABSTRACT

Efforts to understand the underlying mechanisms driving changes in gene expression have focused predominantly on genetic and epigenetic influences on transcription mediated by alterations in signal transduction pathways, their transcription factors, or gene promoter elements and associated chromatin structure. However, recent studies have emerged that also highlight the impact of post-transcriptional regulation of gene expression. Post-transcriptional influences mediated by microRNA (miRNA) play a major role in coordinating the regulation of gene expression during the differentiation and development of the brain. This study has established the specific patterns miRNA expression throughout neuronal differentiation, normal human brain development and schizophrenia.

Using a custom microarray, miRNA expression was examined in differentiating neuroblasts *in vitro*. This revealed that the entire miR-17 family of miRNA displayed reduced expression in response to the differentiation process and was shown to target several known neuronal markers. This result suggested that the miR-17 family might be working co-operatively to fine tune the gene expression changes taking place in the neuronal differentiation process. miRNA expression was also examined in human neurodevelopment. These results demonstrated that a large proportion of miRNA displayed distinct expression changes with age and are likely to be responsible for many of the gene expression changes observed during brain maturation and throughout aging. Perhaps even more significantly, miRNA expression profiling of postmortem brain in the superior temporal gyrus and dorsolateral prefrontal cortex revealed an increase in miRNA expression and biogenesis that suggested a role for miRNA expression in the neuropathology of schizophrenia.

The findings presented in this thesis support mounting evidence that miRNA play a crucial role in the regulation of gene expression in normal neurodevelopment and alterations to miRNA expression contributes to the pathogenesis of schizophrenia.

# LIST OF ABBREVIATIONS

| | |
|---|---|
| **3'-UTR** | 3' untranslated region |
| **Ago** | Argonaute |
| **BDNF** | brain-derived neurotrophic factor |
| ***C. elegans*** | *Caenorhabditis elegans* |
| **CAMK2γ** | Calcium/calmodulin-dependent protein kinase type II gamma |
| **CLOCK** | Circadian Locomotor Output Cycles Kaput |
| **CNV** | copy number variant |
| **CREB** | cAMP response element-binding |
| **DGCR8** | DiGeorge critical region 8 |
| **DISC1** | Disrupted in schizophrenia 1 |
| **DLPFC** | dorsolateral prefrontal cortex |
| **DNA** | deoxyribonucleic acid |
| **ERBB4** | Receptor tyrosine-protein kinase erbB-4 |
| **FEZ1** | Fasciculation and elongation protein zeta-1 |
| **FMR1** | fragile X mental retardation 1 |
| **FMRP** | fragile X mental retardation protein |
| **GABA** | γ-Aminobutyric acid |
| **GWAS** | genome-wide association study |
| **IRES** | internal ribosome entry site |
| **LIMK1** | Lim-domain-containing protein kinase 1 |
| **MECP2** | methyl CpG binding protein 2 (Rett syndrome) |
| **miRNA** | microRNA |
| **mRNA** | messenger RNA |
| **NDEL1** | Nuclear distribution protein nudE-like 1 |
| **NMDA** | N-Methyl-D-aspartic acid |
| **NRG1** | neuregulin-1 |
| **P bodies** | processing bodies |
| **PABP** | polyA binding protein |
| **PDE4B** | cAMP-specific 3',5'-cyclic phosphodiesterase 4B |
| **pre-miRNA** | precursor miRNA |
| **pri-miRNA** | primary miRNA |
| **PTBP1** | Polypyrimidine tract-binding protein 1 |
| **REST** | RE1-Silencing Transcription factor |
| **RISC** | RNA induced silencing complex |
| **RNA** | ribonucleic acid |
| **RNAi** | RNA interference |
| **rRNA** | ribosomal RNA |
| **siRNA** | short-interfering RNA |
| **SLITRK1** | SLIT and NTRK-like family, member 1 |
| **SNP** | single nucleotide polymorphism |
| **STG** | superior temporal gyrus |
| **tRNA** | transfer RNA |