



# Transcriptome Analyses of Human Autistic Brain Tissue

A COMPLEMENTARY METHOD TO AID IDENTIFICATION OF AUTISM  
SUSCEPTIBILITY GENES

## EXECUTIVE SUMMARY

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## The Cooperative Research Centre for Living with Autism (Autism CRC)

The Cooperative Research Centre for Living with Autism (Autism CRC) is the world's first national, cooperative research effort focused on autism. Taking a whole of life approach to autism focusing on diagnosis, education and adult life, Autism CRC researchers are working with end-users to provide evidence-based outcomes which can be translated into practical solutions for governments, service providers, education and health professionals, families and people with autism.

[autismcrc.com.au](http://autismcrc.com.au)

# Transcriptome Analyses of Human Autistic Brain Tissue

The human genome is made up of DNA (deoxyribonucleic acid). DNA contains the instructions needed to build and maintain cells. For the instructions to be carried out, DNA must be "read" and transcribed or copied into RNA (ribonucleic acid). These gene readouts are called *transcripts*, and a *transcriptome* is a collection of all the gene readouts in a single cell.

An RNA sequence mirrors the sequence of the DNA from which it is read. By analysing the *transcriptome* researchers can determine when and where each gene is turned 'on' or 'off' in the cells and tissues of an organism. By collecting and comparing these readouts of different types of cells, researchers can understand how that type of cell normally functions, and how changes in the normal level of gene activity may reflect or contribute to disease. The function of most genes is not yet known. A search of a transcriptome database can give researchers a list of all the tissues in which a gene is expressed, providing clues about its possible function.

<https://www.genome.gov/13014330/transcriptome-fact-sheet/>

## PURPOSE OF THIS STUDY

This study aimed to use *gene expression data* to identify causal genetic variants (differences) identified by exome sequencing. Gene expression is the process by which information from a gene is used in the synthesis of a functional gene product (typically a protein or functional RNA). Exome sequencing is a technique for arranging the expressed genes in a genome.

## STUDY DESCRIPTION

We analysed gene expression data from 74 autistic post-mortem brain samples and integrated these data with pilot exome sequencing data from <http://www.ncbi.nlm.nih.gov/pubmed/24893065>.

Given the limited size of this dataset, and the changes made to the CRC genetics program so that no further exome sequencing will be generated, we focussed on a syndromic form of autism for which the underlying mutation is well known (Rett Syndrome). The results of these transcriptome analyses are published in Lin et al. BMC Genomics 2016.

## DATA ANALYSIS

Paired and RNA-seq data were mapped to the human genome (hg19) using the Tphat spliced aligner. Gene-level counts were obtained using the

featureCounts function in the Rsubread Bioconductor package. Statistical significance was assessed using the EdgeR Bioconductor software.

## SUMMARY OF FINDINGS

Our results are currently descriptive, as we did not have large enough samples with exome sequencing data to assess statistical significance.

In Rett Syndrome, we identified increased expression of the C1Q complex genes (C1QA, C1QB, C1QC) in post-mortem tissue, indicating a potential excess of *microglial activation* in this form of autism. *Microglia* are a type of glial cell located in the brain and spinal cord. They act as the main form of active immune defence in the central nervous system (CNS). Microglia protect the immune system and protect the brain and spinal cord against viruses, bacteria or other organisms.

*Microglial abnormalities* have been shown to be involved in Rett Syndrome, as well as autism of unknown cause, suggesting that brain-specific immune/inflammatory responses may be a potential future therapy in ASD. Activation of the microglial cells is a sign of disease processes occurring in the brain.

## IMPLICATIONS/RECOMMENDATIONS

Further studies combining transcriptomic (gene read outs), epigenomic (environmental factors that switch genes on and off) and whole genome sequencing analysis of brain samples are needed to evaluate the outcomes of genetic variation in autism.

This direction is actively pursued by the PsychENCODE consortium (<http://psychencode.org/>) and thus Autism CRC might benefit from integrating the results of SNP data with PsychENCODE data.