The importance of Gene Expression in Neurodegenerative Disease Research

Scientific review of the value of gene expression for identifying biomarkers, developing signatures, and understanding the pathogenesis and progression of neurodegenerative diseases.

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Trends in Neurodegenerative Disease Research

Neurodegenerative diseases represent a growing health concern and economic burden as the aging population increases and disease rates soar. The World Health Organization's 2006 report on Neurological disorders states that the rates of Alzheimer's disease (AD) and other dementias are projected to increase by 66% between 2005 to 2030[1], while the Centers for Disease Control (CDC) report that death rates from AD have already increased 55% between 1999 and 2014 (CDC May 2017 Morbidity and Mortality Weekly Report). These and other similar statistics serve as a call to action for the medical and research communities and create a sense of urgency for new discoveries leading to increasing insights into disease mechanisms, biomarker and therapeutic developments and improved diagnostic tests.

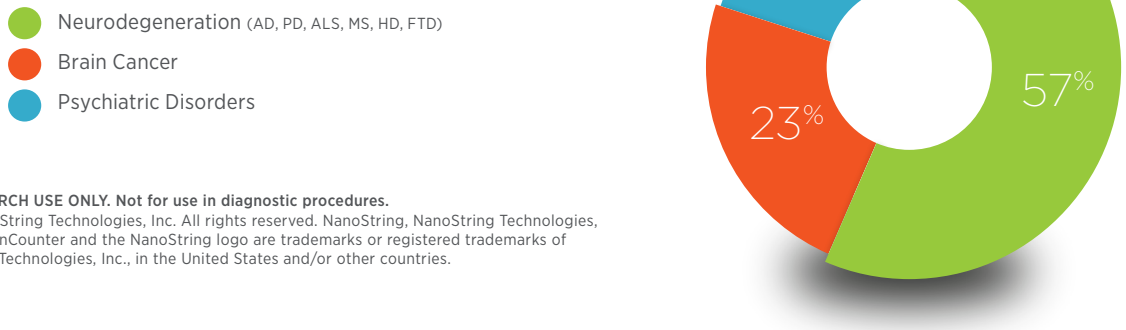
In recent years, the fields of clinical neurology and basic neuroscience have benefitted from advanced molecular techniques, as well as improved diagnostic tests and disease management. Despite these strides, the field still lags behind that of other disciplines, such as oncology, cardiology and endocrinology, due in part to the relative inaccessibility of the brain during life and the high degree of neurodegenerative disease heterogeneity. NanoString's molecular barcoding technology is well-positioned to address the challenges faced by neurodegenerative disease researchers including limited and challenging sample types, data reproducibility, and ease of data analysis. This is evidenced by the growing body of publications demonstrating the research utility of the nCounter® Analysis System to reveal biological insights from challenging samples across a variety of neurological disorders (Figure 1 and Figure 2).

Gene Expression in Neurological Disease

Pathway-based gene expression studies have proven valuable when studying complex diseases, both in providing a framework for comprehensive measurement of biological mechanisms and in establishing potentially prognostic and predictive signatures of disease progression and drug response. Recent gene expression studies have implicated biological pathways such as inflammation, protein homeostasis, RNA splicing, and mitochondrial fidelity as key in the development and progression of multiple neurodegenerative disorders, such as amyotrophic lateral sclerosis (ALS)[2], Parkinson's disease (PD)[3,4] and Alzheimer's disease (AD)[4,5]. NanoString Technologies provides customizable panels that allow for the analysis of up to 800 RNA, DNA, or Protein targets, encompassing multiple pathways from a single sample. With limited sample types, particularly from human specimens, extracting the maximal amount of relevant information from each sample is critical. Researchers have demonstrated the power of the nCounter gene expression platform to generate robust results from CNS tissue[7], as well as peripheral blood[6] and induced pluripotent stem cells[7,8]. Because the nCounter platform does not require amplification or the use of enzymes, challenging samples like post-mortem FFPE tissue can also be reliably analyzed to yield reproducible results. Moreover, NanoString offers solutions for single cell and low input samples aimed at getting the most biological information from the smallest sample. In contrast to other technologies that often require extended bioinformatics analysis, NanoString's simple digital read-outs and data analysis tools put the biological understanding back in the researcher's hand and serve to expedite the time from experimental design to discovery.

FIGURE 1

Neurological Disorder Publications Using NanoString nCounter



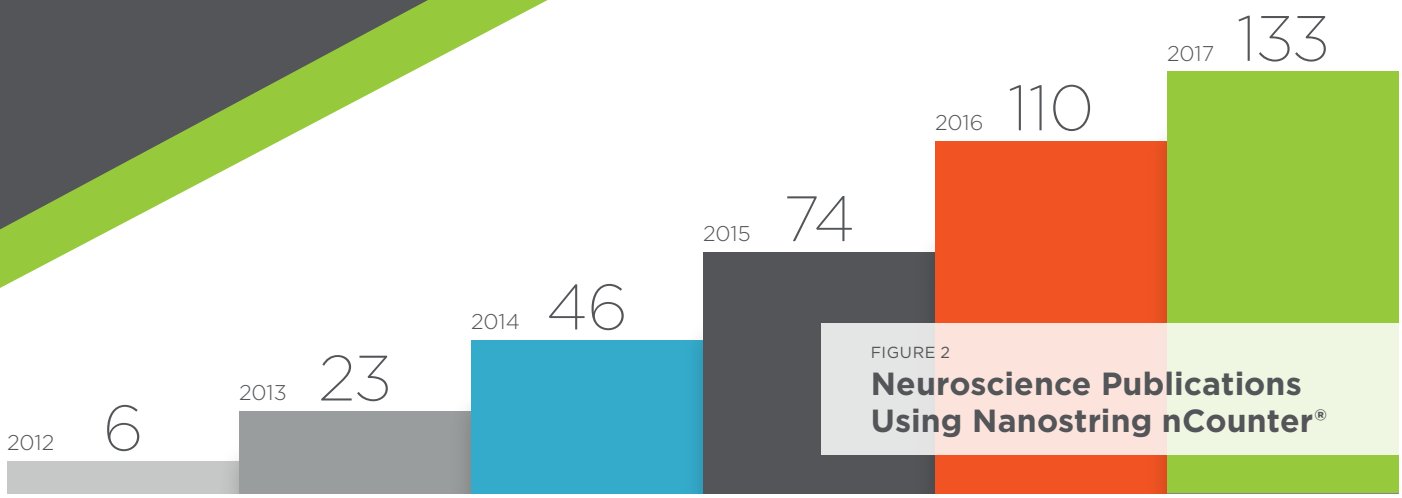


FIGURE 2
Neuroscience Publications Using Nanostring nCounter®

Combining Gene Expression and Protein Analysis

Given that many neurodegenerative diseases manifest pathologically as proteopathies, it is understandable that much emphasis has been placed on direct investigation of proteins. These studies have been key in understanding the mechanisms of protein aggregation and developing strategies to prevent, mitigate, and reverse aberrant protein accumulations in the nervous system. Thanks to genome-wide association studies, increasing numbers of disease causing genes are being identified allowing for investigation into the function of corresponding mutant proteins, thus highlighting the importance of complementary genetic and biochemical analyses in the study of neurodegenerative disease pathogenesis. Many of these studies have uncovered additional roles for RNA processing and splicing, revealing another layer of dysfunction in neurodegeneration. Furthermore, the RNA processing defects and other pre-translational modes of regulation make the combined measurement of protein and RNA crucial, as the full understanding of disease at the molecular level requires all intermediates between genotype and phenotype[9]. NanoString has recently introduced 3D Biology™ assays which enable multi-analyte (i.e. RNA, DNA and Protein) multiplex analysis of key pathways in immune response and solid tumor progression (nanostring.com/3D). Future developments involve the ability to spatially resolve and simultaneous quantitate RNA and protein on a single platform, empowering a unique method for digital counting of both analytes from a single sample (nanostring.com/DSP).

Identification of Biomarkers and Personalized Medicine

Modern genomics technologies have advanced considerably in recent years and are proving critical in addressing the challenges of neurogenerative disease diagnosis and research. Looking beyond disease diagnosis to disease management as new neurodegenerative disease treatments are tested and developed, there is an even greater need to understand various mechanisms of response or resistance to treatments. More robust technology and wide-spread accessibility has expanded the reach to an increasing number of scientists who are using gene expression profiling to better understand mechanisms of disease and treatment response. Gene expression profiling has the potential to support the next step forward in neurodegenerative research, allowing for the identification of biomarkers of disease that will allow for early diagnosis, classification of disease heterogeneity and ultimately, precision medicine on par with that currently available for cancer patients. NanoString has a mission to enable precision medicine through translational research with active partnerships with the research community for the development of biomarkers and gene expression signatures[10,11].

For more information on NanoString's neuroscience research products and publications, visit nanostring.com/neuroscience

REFERENCES

1. World Health Organization, Neurological disorders: public health challenges, ISBN 92 4 1563362 (NLM classification: WL 140), 2006.
2. Kiskinis E. et al., "Pathways disrupted in human ALS motor neurons identified through genetic correction of mutant SOD1." Cell Stem Cell. April 03, 2014
3. Mariani, E. et al., Meta-Analysis of Parkinson's Disease Transcriptome Data Using TRAM Software: Whole Substantia Nigra Tissue and Single Dopamine Neuron Differential Gene Expression. PloS One 11, e0161567 (2016)
4. Chen, W. et al., Role of neuroinflammation in neurodegenerative diseases, Molecular Medicine Reports, February 2016 DOI: 10.3892/mmr.2016.4948
5. Spangenberg E.E. et al., "Eliminating microglia in Alzheimer's mice prevents neuronal loss without modulating amyloid-β pathology." Brain. February 26, 2016
6. Locascio J.J. et al., "Association between a-synuclein blood transcripts and early, neuroimaging-supported Parkinson's disease." Brain. July 28, 2015
7. Labonté B. et al., "Sex specific transcriptional signatures in human depression.", Nature Medicine. Published online 21 August 2017; doi:10.1038/nm.4386
8. Ramanan, V. K. et al., "Pathways to neurodegeneration: mechanistic insights from GWAS in Alzheimer's disease, Parkinson's disease and related disorders", Am J Neurodegner Dis 2013:2 (3): 145-175
9. Seyfried, N.T. et al., "A Multi-network Approach Identifies Protein-Specific Co-expression in Asymptomatic and Symptomatic Alzheimer's Disease", Cell Systems 4, 60-72, January 25, 2017
10. Ayers, Mark, et al. "IFN-γ-related mRNA profile predicts clinical response to PD-1 blockade." The Journal of Clinical Investigation 127.8 (2017)
11. Scott D.W. et al., Determining cell-of-origin subtypes of diffuse large B-cell lymphoma using gene expression in formalin-fixed paraffin embedded tissue., Blood, Jan 07, 2014

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