Emerging bioinformatics approaches for analysis of NGS-derived coding and non-coding RNAs in neurodegenerative diseases.

By ppollins
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By ppollins January 28, 2015


Abstract:

Neurodegenerative diseases in general and specifically late-onset Alzheimer's disease (LOAD) involve a genetically complex and largely obscure ensemble of causative and risk factors accompanied by complex feedback responses. The advent of "high-throughput" transcriptome investigation technologies such as microarray and deep sequencing is increasingly being combined with sophisticated statistical and bioinformatics analysis methods complemented by knowledge-based approaches such as Bayesian Networks or network and graph analyses. Together, such "integrative" studies are beginning to identify co-regulated gene networks linked with biological pathways and potentially modulating disease predisposition, outcome, and progression. Specifically, bioinformatics analyses of integrated microarray and genotyping data in cases and controls reveal changes in gene expression of both protein-coding and small and long regulatory RNAs; highlight relevant quantitative transcriptional differences between LOAD and non-demented control brains and demonstrate reconfiguration of functionally meaningful molecular interaction structures in LOAD. These may be measured as changes in connectivity in "hub nodes" of relevant gene networks (Zhang etal., 2013). We illustrate here the open analytical questions in the transcriptome investigation of neurodegenerative disease studies, proposing "ad hoc" strategies for the evaluation of differential gene expression and hints for a simple analysis of the non-coding RNA (ncRNA) part of such datasets. We then survey the emerging role of long ncRNAs (IncRNAs) in the healthy and diseased brain transcriptome and describe the main current methods for computational modeling of gene networks. We propose accessible modular and pathway-oriented methods and guidelines for bioinformatics investigations of whole transcriptome next generation sequencing datasets. We finally present methods and databases for functional interpretations of IncRNAs and propose a simple heuristic approach to visualize and represent physical and functional interactions of the coding and non-coding components of the transcriptome. Integrating in a functional and integrated vision coding and ncRNA analyses is of utmost importance for current and future analyses of neurodegenerative transcriptomes.

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