Long non-coding RNA and alternative splicing modulations in Parkinson's leukocytes identified by RNA sequencing.

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Abstract:

The continuously prolonged human lifespan is accompanied by increase in neurodegenerative diseases incidence, calling for the development of inexpensive blood-based diagnostics. Analyzing blood cell transcripts by RNA-Seq is a robust means to identify novel biomarkers that rapidly becomes a commonplace. However, there is lack of tools to discover novel exons, junctions and splicing events and to precisely and sensitively assess differential splicing through RNA-Seq data analysis and across RNA-Seq platforms. Here, we present a new and comprehensive computational workflow for whole-transcriptome RNA-Seq analysis, using an updated version of the software AltAnalyze, to identify both known and novel high-confidence alternative splicing events, and to integrate them with both protein-domains and microRNA binding annotations. We applied the novel workflow on RNA-Seq data from Parkinson's disease (PD) patients' leukocytes pre- and post- Deep Brain Stimulation (DBS) treatment and compared to healthy controls. Disease-mediated changes included decreased usage of alternative promoters and N-termini, 5'-end variations and mutually-exclusive exons. The PD regulated FUS and HNRNP A/B included prion-like domains regulated regions. We also present here a workflow to identify and analyze long non-coding RNAs (lncRNAs) via RNA-Seq data. We identified reduced lncRNA expression and selective PD-induced changes in 13 of over 6,000 detected leukocyte lncRNAs, four of which were inversely altered post-DBS. These included the U1 spliceosomal lncRNA and RP11-462G22.1, each entailing sequence complementarity to numerous microRNAs. Analysis of RNA-Seq from PD and unaffected controls brains revealed over 7,000 brain-expressed lncRNAs, of which 3,495 were co-expressed in the leukocytes including U1, which showed both leukocyte and brain increases. Furthermore, qRT-PCR validations confirmed these co-increases in PD leukocytes and two brain regions, the amygdala and substantia-nigra, compared to controls. This novel workflow allows deep multi-level inspection of RNA-Seq datasets and provides a comprehensive new resource for understanding disease transcriptome modifications in PD and other neurodegenerative diseases.

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