Profiling the promoterome of the human brain

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Research question and background

The human brain is divided into distinct anatomical districts, characterized by different cellular compositions and functions and interconnected by complex communication networks. Differences in transcription are likely to play a major role in the establishment and maintenance of the morphological and functional differences observed across different brain regions.
Aiming to build a complete promoter map to uncover the transcriptional regulatory networks defining the human brain we have used the data we generated as part of the Fantom5 consortium. The Fantom 5 consortium coupled Cap analysis of gene expression (CAGE) technology to next generation sequencing of single cDNA molecules to map transcription start sites (TSSs) and their usage in human and mouse primary cells, cell lines and tissues to produce a comprehensive overview of gene expression across the human body.

Methods and tissues used

We profiled 15 regions of the human central nervous system (CNS), using post mortem tissue from three aged adult donors (spinal cord, temporal cortex, frontal cortex, parietal cortex, occipital cortex, cerebellum, medulla oblongata, hippocampus, putamen, caudate, thalamus, amygdala, substantia nigra, globus pallidus, locus coeruleus).
Total RNA was extracted and purified from tissues using the Trizol tissue kit and RNA quality was assessed using the RNA Integrity Number (RIN). CAGE libraries where then prepared for each tissue. All the libraries were sequenced using the Heliscope single molecule sequencer.

Results and conclusion

We created a high-resolution atlas of transcription start sites for 15 anatomical regions of the CNS showing that it is characterized by a significantly higher transcriptional complexity with a unique expression signature, clearly distinguishable from other tissues and not limited to protein coding genes but extending to lncRNAs and novel transcripts.
We observed that transcripts up-regulated in brain arise in a specific transcriptional context, being more often transcribed from CG rich regions, simple and low complexity repeats.
We assessed the extent of regionally biased transcription across distinct regions of the adult brain, highlighting a set of locally expressed lncRNAs and transcription factors that might have an important role in brain-specific transcriptional regulation.
We have identified a set of 183 transcription factors and 206 lncRNAs up-regulated in brain which co-expression patterns identify super-groups of regions with related function/developmental derivation.
Due to its high-resolution and the large variety of CNS regions represented, this study provides an invaluable resource for understanding region-specific transcriptional regulation.