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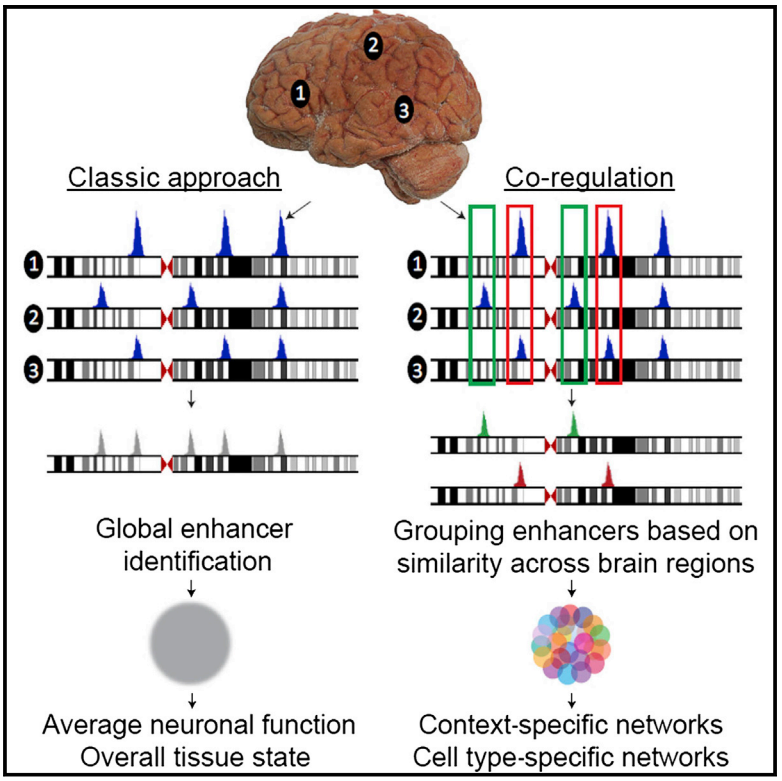
Large-Scale Identification of Coregulated Enhancer Networks in the Adult Human Brain

Graphical Abstract



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In Brief

Epigenomic analysis of complex tissues such as the human brain has been hampered by their significant heterogeneity. However, cell culture systems and model organisms generally do not correctly represent the epigenome as it is in vivo. In this study, Vermunt et al. use large-scale ChIP-sequencing analysis to map active regulatory elements in the human brain. Analyzing activity patterns across different anatomical regions enables the identification of enhancer networks that provide cell-type and context-specific in vivo information.

Highlights

Genome-scale enhancer identification is done in 136 regions of the adult human brain

Enhancer enrichment varies across anatomical regions

Coregulated enhancers represent cell type- and context-specific networks

Alterations in newly identified enhancers are linked to Parkinson's disease risk

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Large-Scale Identification of Coregulated Enhancer Networks in the Adult Human Brain

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SUMMARY

Understanding the complexity of the human brain and its functional diversity remain a major challenge. Distinct anatomical regions are involved in an array of processes, including organismal homeostasis, cognitive functions, and susceptibility to neurological pathologies, many of which define our species. Distal enhancers have emerged as key regulatory elements that acquire histone modifications in a cell- and species-specific manner, thus enforcing specific gene expression programs. Here, we survey the epigenomic landscape of promoters and *cis*-regulatory elements in 136 regions of the adult human brain. We identify a total of 83,553 promoter-distal H3K27ac-enriched regions showing global characteristics of brain enhancers. We use coregulation of enhancer elements across many distinct regions of the brain to uncover functionally distinct networks at high resolution and link these networks to specific neuroglial functions. Furthermore, we use these data to understand the relevance of noncoding genomic variations previously linked to Parkinson's disease incidence.

INTRODUCTION

Understanding the human brain is one of the key challenges of biology. Over 100 different anatomical structures are connected by billions of neurons and glia into a functional network that regulates tissue homeostasis throughout the body while also determining our cognitive state (Nolte, 2009). Functionally distinct anatomical regions have evolved in a species-specific manner, giving rise to the defining physical and cognitive features that separate humans from other species (Konopka and Geschwind, 2010). Microarray analyses on distinct regions of the human brain have demonstrated that gene expression profiles vary significantly across adult brain structures (Colantuoni et al., 2011; Hawrylycz et al., 2012; Kang et al., 2011). The nature of these variations in gene expression and their implications in neuronal plasticity are currently subjects of intense investigation.

The epigenetic landscape that imposes these gene expression programs is regulated by transcription factors that alter local chromatin state of the genome at functional regulatory elements (e.g., enhancers and promoters). During development of the brain, progressive epigenetic alterations of the genome are involved in establishing specific functional regions (Dulac, 2010). Indeed, variations in the levels of individual transcription factors that drive these epigenetic alterations can affect functional regionalization as well as the laminar identity of cells within a given cortical region (Sur and Rubenstein, 2005). As the epigenome is influenced by environmental factors, it functions at the intersection between the genome and its developmental and environmental history. Charting the epigenome has provided crucial information on how a cell uses the epigenome to store memories of environmental events (Ostuni et al., 2013). Furthermore, it allowed the stratification of inactive gene expression states into primed/poised (ready for activation) or silent (Bernstein et al., 2006), which provides unique information on a cell's transcriptional potential.

While the core promoter of a gene constitutes the site where the transcriptional initiation complex is formed, enhancer elements are defined as regions in the genome that regulate core-promoter activity independent of distance or orientation (Maston et al., 2006). The distinction between proximal enhancers that are often coined as part of the promoter (or proximal promoter) and enhancers that are more distal is vague, but both can be considered part of the promoter as a whole. Enhancers in particular have been shown to support core promoter activity in a tissue- and species-specific manner, thus enforcing specific gene expression programs that shape the biological state of the cell (Bulger and Groudine, 2011). Enhancers can be characterized on a global scale using distinct epigenetic footprints that are typically found to display this cell type- and species-specific distribution and contain important information on how and why certain cellular states are reached (Creyghton et al., 2010; Heintzman et al., 2009; Rada-Iglesias et al., 2011; Visel et al., 2009). This information is typically missed in genome sequencing and transcriptomic studies. More recent efforts have also focused on the identification of enhancers using enhancer RNAs (eRNAs) (Andersson et al., 2014). However, this analysis