Spatiotempotal properties of NDD genes during brain development for biomarker discovery

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What would the reader gain from this lit review

The reader will have understanding of the following:

- Introduction to brain development
- Introduction to neurodevelopmental disorders
- Introduction to sequencing technologies for gene expression studies
- an understanding of how gene expression studies contribute to our knowledge of brain development and NDDs
- Available resources

1 Aims of the project

- To comprehensively characterize the expression properties of ID and CP enes in the normal human brain
  - To determine whether ID and CP genes are expressed in a cell-type speciic mannner using single-cell RNA-seq data
  - To characterize the developmental trajectory of gene expression for ID and CP genes and assess their expression during cellular maturation in brain organiods and assess their expression across multiple fetail developmental periods
  - To characterize the spatial and temporal properties of ID and CP gene expression in the adult brain, by assessing age-dependent changes brain-region and cortical layer-specificity
- To determine whether convergent gene expression changes are observed in ID and CP in patient-derived cells with heterogenous mutations

2 Introduction

Human brain development is a complex and a tightly regulated process during which changes occur at both anatomical and functional levels. The processes of brain development are highly dependent on the appropriate expression of RNA and proteins, Mutations that result in altered expression or function of these gene products can cause or contribute to neurodevelopmental disorders (NDDs).

3 Neurodevelopmental disorders

Neurodevelopmental disorders (NDDs) are a group of early onset neurological disorders affecting an estimated 10% to 15% of the population. Common NDDs include autism spectrum disorders, intellectual disability, epilepsy, motor/tic movement disorders among others.

Common NDDs include autism spectrum disroder, intellectual disability, epilepsy and motor/tic movement disorders, and are characterized by strong clinical co-morbidity which suggests common genetic etiology.

- ASD and how many genes have been identified
- ID and how many genes have been identified
- Other NDDs and how many genes have been identified

The genetic heterogeneity and overlap observed in NDDs make it difficult to identify the genetic causes of specific clinical symptoms

Autism

Autism spectrum disorders represent genetically heterogeneous group of neurodevelopmental syndromes with high prevalence that has a wide range of phenotype. While there is no

unifying hypothesis about the molecular pathology of autism, it is clear that the disorder is highly hertiable and results from the combination of genetic, neurologic , immunologic and environmental factors.

Recent advnces in sequencing technologies have made it possible to gain insight into the molecular aspects of ASD. Microarray technologies and next-generation sequencing have enabled high-throughput discovery of genes likely to be involved in the molecular pathology of autism.5, 6, 7, 8 However, as the success in discovery has risen, the number of candidate genes with associated risk for ASD has also stretched well into the hundreds.9, 10 As of December 2014, 667 genes have been implicated in autism. Despite the large amounts of data now available, the general lack of replication across studies suggests that more data will be needed to fully characterize the genetic models responsible for the various forms of autism.

3.1 Heterogeneity of NDDs

4 Expression studies

4.1 RNA: bulk vs single-cell

The human brain contains billions of highly differentiated and interconnected cells that form intricate neural networks and collectively control the physical activities and high-level cognitive functions, such as memory, decision-making, and social behavior. Big data is required to decipher the complexity of cell types, as well as connectivity and functions of the brain. The newly developed single-cell sequencing technology, which provides a comprehensive landscape of brain cell type diversity by profiling the transcriptome, genome, and/or epigenome of individual cells, has contributed substantially to revealing the complexity and dynamics of the brain and providing new insights into brain development and brain-related disorders.

The development of single-cell technologies, especially single-cell RNA-sequencing (scRNA-

seq), has provided new opportunity to address this challenge by looking through transcriptomic profile of each individual cell. Since the first introduction of scRNA-seq technique by Tang et al. in 2009. In recent years, a dozen of scRNA-seq studies that look into the cellular composition, heterogeneity, and disease-specific populations in mammalian brain has also demonstrated the power of this technology in addressing the challenges in understanding the complexity, connectivity, and functions of brain cell types

4.2 Co-expression network analysis

5 Characterisation of brain diversity using single-cell

5.1 Studies that have characterized the single-cell transcriptome in the brain

what to review

- human brain single cell rna-seq studies
- reread papers used for PhD proposal
- number and types of samples
- method used for sequencing
- data availablity
- main conclusions of the studies

Year Cells reported Method Technique Species Cell isolation Brain region Developmental stag
2014

- co-expression networks and their utility in spatiotemporal studes
- this kind of analysis in other areas (particularly cancer)
- Use of single-cell analysis vs bulk rna-seq
- what are the datasets available
- where am i going to get the genelists from
- what gene ontologies am I getting with my genes
- current co-expression networks that are available
- lack of ID gene networks
- benchmark potentially?
- Issues with bulk rna?