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A novel computational framework for inferring the developmental and cellular origins of rare and congenital disorders using scRNA-seq data

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Keywords

Phenotype, Mutation, Gene Expression

Abstract

Despite their devastating impacts on millions of people, most rare and congenital disorders remain poorly understood, leaving the patients with these disorders with no FDA-approved treatment. To inform the development of treatments for these diseases, it is crucial that we understand their root cause. Therefore, we propose the development of two novel computational pipelines to discover the cellular etiology of diseases. Based on the well-supported observation that disorders with a shared phenotype arise from overlapping molecular processes, we hypothesize that these processes are, in many cases, localized to a small set of cell types at specific developmental stages. For our first aim, we will design a novel computational pipeline to discover the cell types whose disrupted intrinsic processes putatively cause a specific phenotype of interest. Our second aim will be devoted to the development of the first computational pipeline for uncovering the pairs of cell types whose disrupted communication initiates the phenotype. In addition, our pipelines will be the first to offer insight into the putative developmental stages at which these cell types are impacted.

A major challenge in studying rare and congenital disorders is the difficulty in collecting disease-specific data. Our focus on shared phenotypes of disorders will eliminate any dependence on knowing the mutated gene for any one disorder, and our pipelines will be designed to use single-cell gene expression data from healthy tissues, eliminating the need to collect samples directly from patients. Our project will provide the research community with a dedicated tool for uncovering the cellular etiology of diseases based on their shared molecular processes.