Single-Cell Transcriptomic Analysis Reveals Genetic Drivers of Slow/Fast Motor Neuron Identity

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Motor neurons are the essential cells connecting the brain and muscles, translating our thoughts and needs into actions and response. Here, we analyze a previously published dataset to explore the gene expression differences that distinguish slow and fast motor neuron subtypes. Surprisingly, we find that the two subtypes do not transcriptionally cluster into separate populations. Rather, we find that all motor neurons exist on a continuous spectrum that corresponds with electrophysiological identity. We establish an individual per-neuron 'Fast Score,' and we show that canonical markers of slow and fast motor neurons exist on opposite ends of this continuous spectrum. This finding challenges the conventional wisdom that slow and fast motor neurons are discrete cell types, instead arguing for a new model of motor neuron identity. Using regression analysis, we explore the hypothesis that transcription factors are responsible for polarizing motor neurons along this continuous spectrum. We discover modules of genes controlling electrophysiological properties of slow and fast motor neurons, affirming our hypothesis that gene expression differences encode functional motor neuron properties. Finally, we granularize our data into transcription factor networks, allowing us to resolve master regulators of cell identity in slow and fast motor neurons. Understanding the regulatory logic that polarizes slow and fast motor neurons holds the potential to unlock interconversion between these disease-relevant cell types. In the future, manipulation of these networks may present viable therapeutic strategies in neuromuscular diseases like amyotrophic lateral sclerosis (ALS) and inform our ability to generate motor neuron subtypes in induced pluripotent stem cell-derived models of disease.