Columbia Technology Ventures

Therapeutic targets for Spinal Muscular Atrophy and Amyotrophic Lateral Sclerosis

Technology #cu15008

Spinal muscular atrophy (SMA) is a pediatric neuromuscular disease characterized by muscle weakness and massive motor neuron loss, which can lead to death by respiratory failure. Amyotrophic Lateral Sclerosis (ALS) is a motor neuron disorder that affects muscle control, leading to muscle spasticity, weakness, speaking and breathing disease. Currently, no effective treatments exist for either SMA or ALS. This technology describes 37 gene variants as possible therapeutic targets that are altered in SMA, as well as several that are altered in ALS. Of these 37 genes, 13 are vulnerability variants (i.e. variants indicative of SMA) and 24 are resistant variants (i.e. variants that confer resistance to SMA). As such, this technology provides a method of treating both diseases or stopping their progression.

Small molecule modulators for effective, versatile treatment of SMA and ALS

This technology achieves the task of identifying over 37 genes that alter the progression of SMA and ALS, all of which can be used to advance therapeutic options for patients. Inhibition of vulnerability genes may reduce susceptibility of motor units to develop SMA, and activation of resistance genes may improve motor unit resistance to develop SMA. One particular gene that is highly correlated with SMA vulnerability is phosphodiesterase 1C (Pde1c). Inhibitors of Pde1c and/or any of the other 12 vulnerability genes could potentially slow or prevent the death of motor neurons in SMA patients. Given that there is no treatment for SMA, if inhibition of any of the vulnerability genes (or conversely, activation of the resistance genes) improves patient quality or length of life, this would be a significant improvement in patient care. Similarly, the ALS-related genes uncovered using this technology indicate both degenerative and protective roles. One of the key ALS-related gene variants discovered using this technology, Phospholipase D1 (PLD1), is strongly correlated with age of ALS onset, and has also been implicated in Alzheimer’s and other neurodegenerative diseases. Small molecule modulators to PLD1 and other ALS risk factor genes are expected to ease and potentially prevent ALS’ most debilitating symptoms.

These therapeutic targets were confirmed in a mouse model of SMA called SMN delta7 mice and in human autopsies of SMA patients; ALS gene variants were uncovered from previously published gene expression data and are now being confirmed in iPS cells.
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Applications:
• Gene variants provide novel therapeutic targets (including Pde1c) to treat or ameliorate SMA progression
• Gene variants linked to SMA resistance provide insight into endogenous mechanisms for slowing or stopping SMA progression
• Investigation of novel therapeutic targets for other neuromuscular diseases
• ALS-linked gene variants (including PLD1) provide novel therapeutic targets for treatment of ALS
• Small molecule inhibitors for PLD1 and other ALS risk factor genes
• Assays for SMA and ALS susceptibility

Advantages:
• Identifies specific gene targets for up-regulation and increased SMA resistance
• Identifies specific gene targets for down-regulation and decreased SMA susceptibility
• Identifies Pde1c as a highly correlated vulnerability gene for development of SMA
• May improve speed and accuracy of testing therapeutics for SMA
• May be valuable in improving SMA patient care
• Identifies PLD1 as a risk factor and a potential therapeutic target in ALS
• Provides small molecule modulators of PLD1 and other genetic risk factors that treat or ameliorate ALS

Patent information:
Patent Pending (WO/2016/054083)
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Related Publications:

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