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Poster P14

An In Vitro Model for Motor Neurons Displays Axonal and Mitochondrial Deficiencies Associated With Charcot-Marie-Tooth Disease Type 2A

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CMT is the most common inherited neuropathy, affecting peripheral sensorimotor nerves, causing muscle weakness, atrophy and pain. CMT2A is the most frequent axonal subtype and an earlier onset form of CMT Type 2. It is associated with mutations in Mitofusin 2 (MFN2), a mitochondrial membrane anchored GTPase involved in equilibrium of mitochondrial fusion/fission. We investigated the impact of the MFN2 R364W mutation on aspects of neuronal cell morphology and mitochondria activity, using microfluidic plates containing compartments to accommodate neuronal elongation. iPSC-derived motor neurons were generated from a healthy human control line and a patient-derived line with the MFN2 R364W mutation and cultured on microfluidic plates to organize neurons into standard reproducible networks with cell bodies positioned in one compartment and axons elongated to a second compartment. Consistent orientation of axons enabled automated imaging/assessment using custom-created software of seven neuromorphological factors including cell size, axonal length, neurite connections, mitochondrial mobility and morphology.

Standardization of neuronal network cultures and analysis with the platform identified key differences between CMT2A and healthy controls, including statistically significant changes in cell number, size, and mitochondrial movement. Non-statistically significant trends were observed for other traits including axonal material, branching, number of branching junctions, axon breadth, and neurite straightness, as well as average anterograde mitochondrial velocity and aspect ratio of upper chamber, neurite channel, and lower chamber mitochondria.

Mouse models for CMT2A are limited. Our study highlights the advantage of using human-derived in vitro models for faster and more effective disease modeling, rapid drug screening, and a deeper understanding of the mechanisms underlying a devastating disease with a huge impact on children's development.