Altered Action Potential waveform and shorter Axonal Initial Segment in hiPSC-derived Motor Neurons with mutations in VRK1

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Novel mutations in VRK1 in a new form of "spinal" CMT (dHMN) with upper motor neuron signs

GENERAL ARTICLE

Loss of Cajal bodies in motor neurons from patients with novel mutations in *VRK1*

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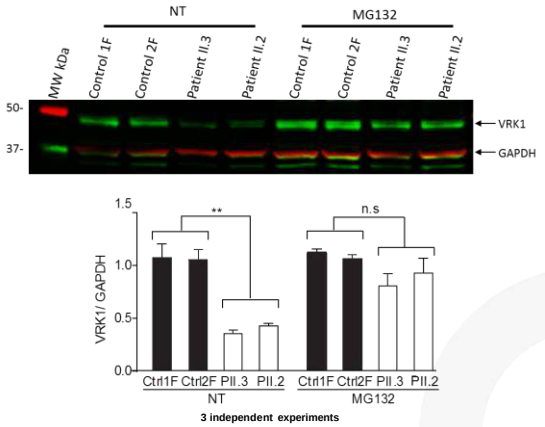
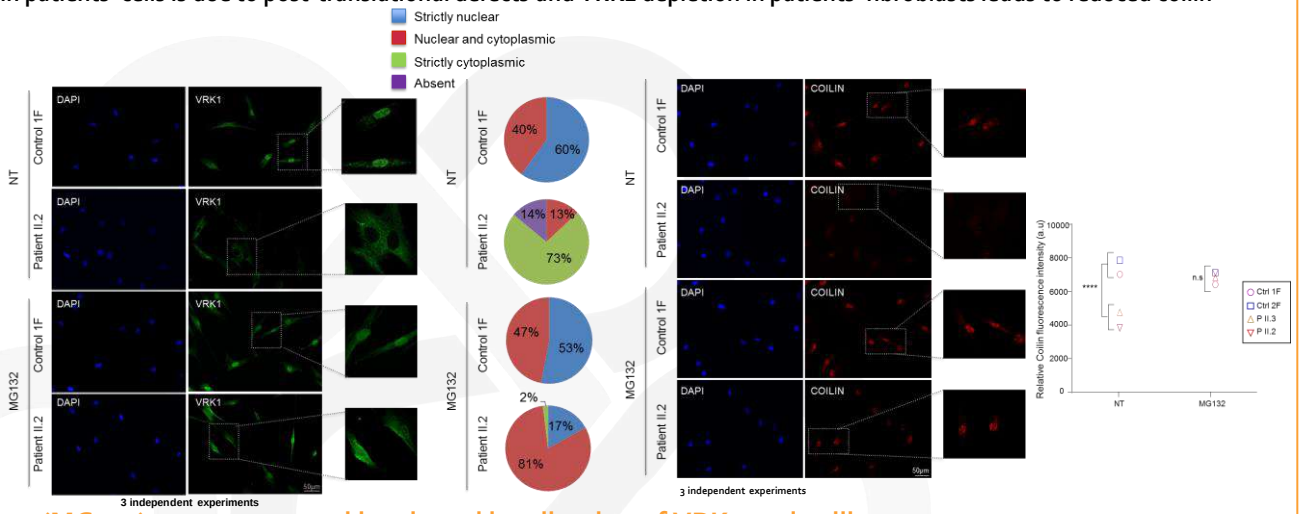
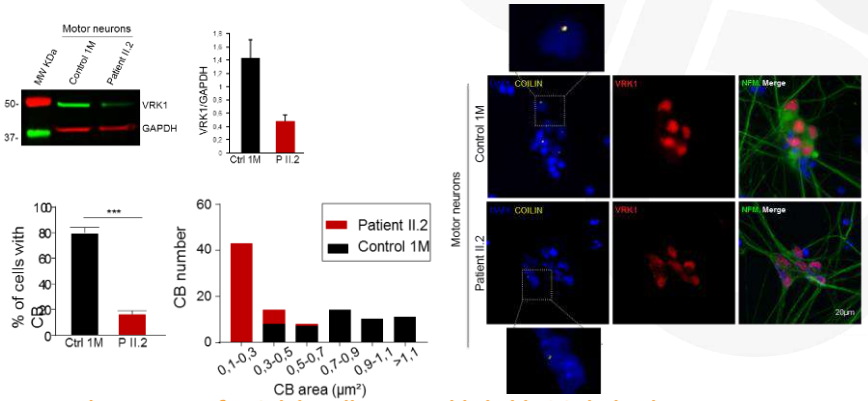
1. In patient's fibroblasts: decrease of VRK1 levels in patients' cells is due to post-translational defects and VRK1 depletion in patients' fibroblasts leads to reduced coilin levels by facilitating its proteasomal degradation.





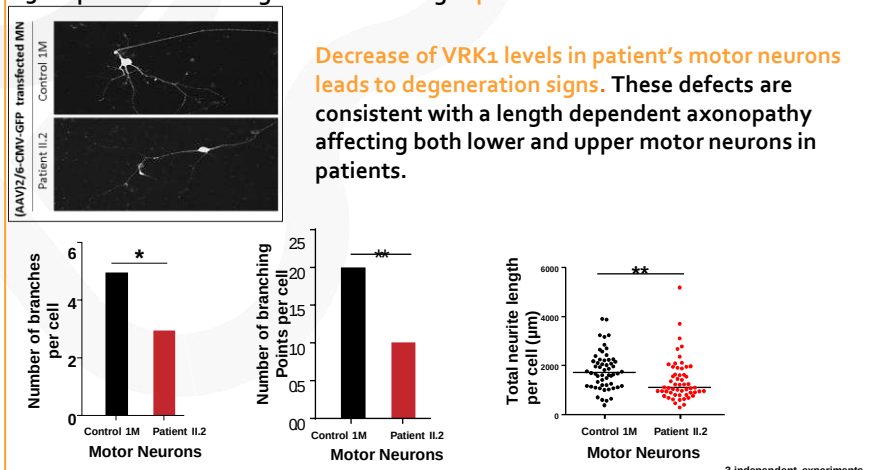
Blockade of the proteasome (MG132) restores normal levels and localization of VRK1 and coilin

2. In patients' hiPSC-derived Motor Neurons (MNs): decrease levels of VRK1 in the nucleus lead to disassembly of Cajal Bodies



VRK1 is necessary for Cajal Bodies assembly in hiPSC-derived MNs

3. Impaired neurite length and branching in patient's hiPSC-derived MNs:

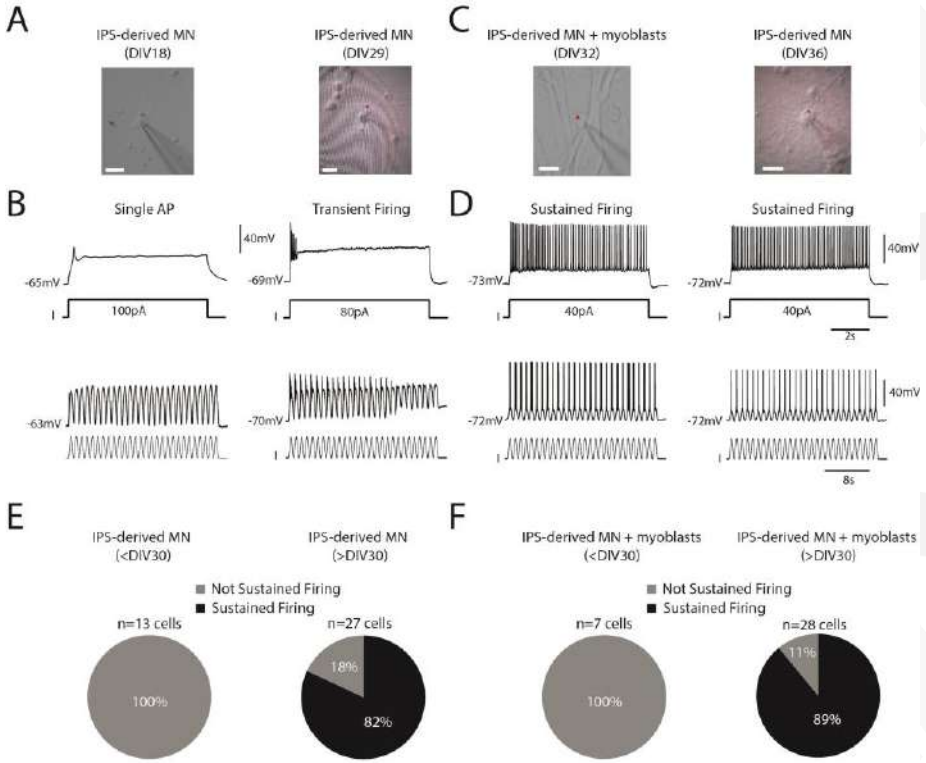


Decrease of VRK1 levels in patient's motor neurons leads to degeneration signs. These defects are consistent with a length dependent axonopathy affecting both lower and upper motor neurons in patients.

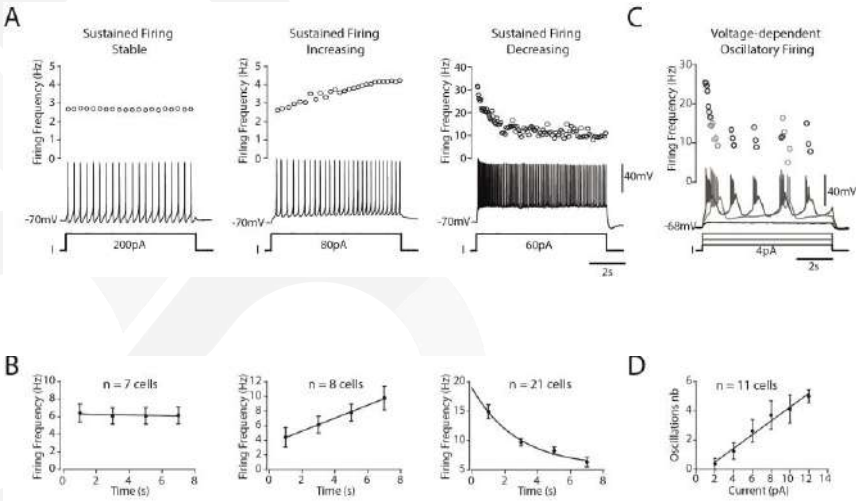
hiPSC-MNs are functional and sustain firing patterns, typical of spinal MNs

hiPSC-derived MNs are functional and sustain firing patterns, typical of spinal MNs

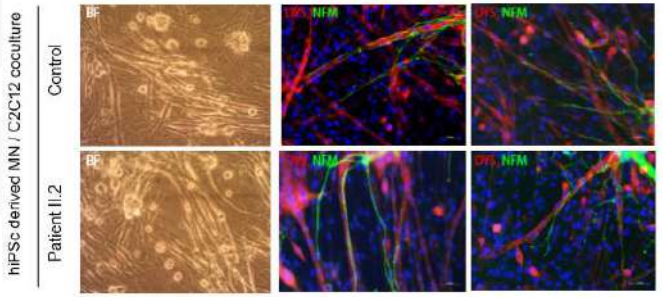
1. Co-culturing human hiPSC-MNs with myoblasts accelerates their functional maturation.



2. Control hiPSC-MNs co-cultured with myoblasts display four distinct electrophysiological signatures



3. Co-culture of control hiPSC-MNs co-cultured with mouse myoblasts



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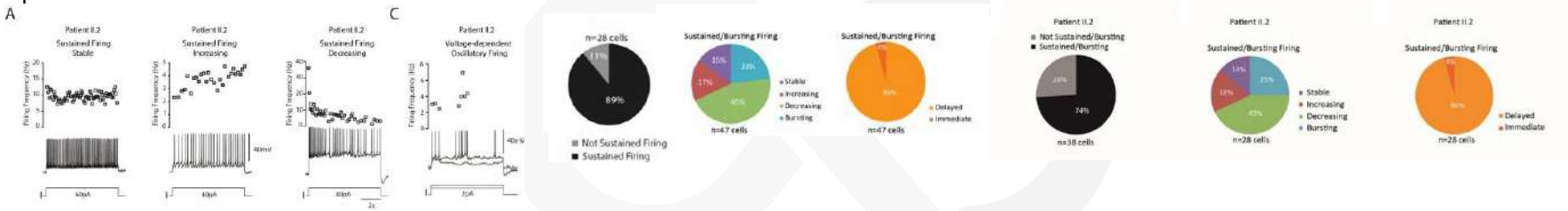
hiPSC-MNs from patients with VRK1 mutations have altered Action Potential waveform and shorter Axonal Initial Segment

1. hiPSC-MNs from patient II.2 display similar electrophysiological firing patterns than controls

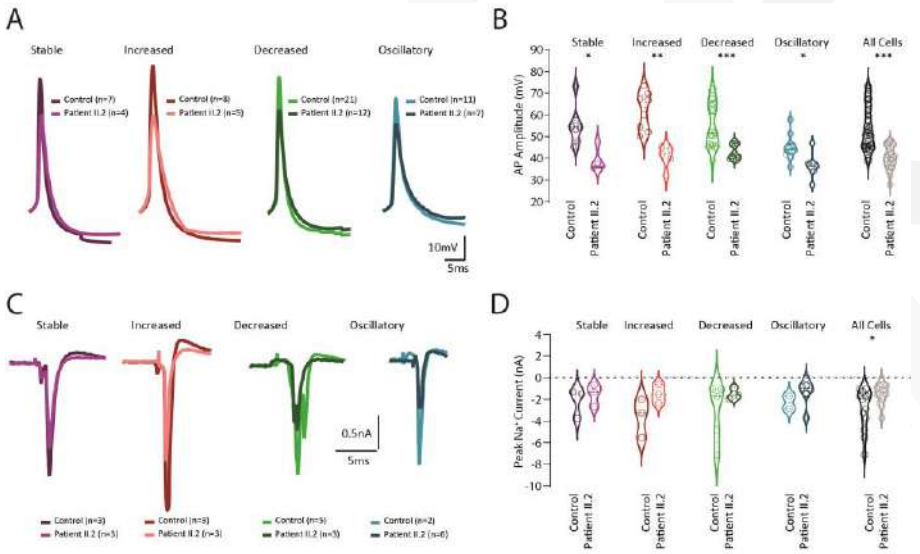
Four distinct electrophysiological signatures obtained in patient II.2 hiPSC-MN

Control hiPSC-MNs with myoblasts (>DIV30)

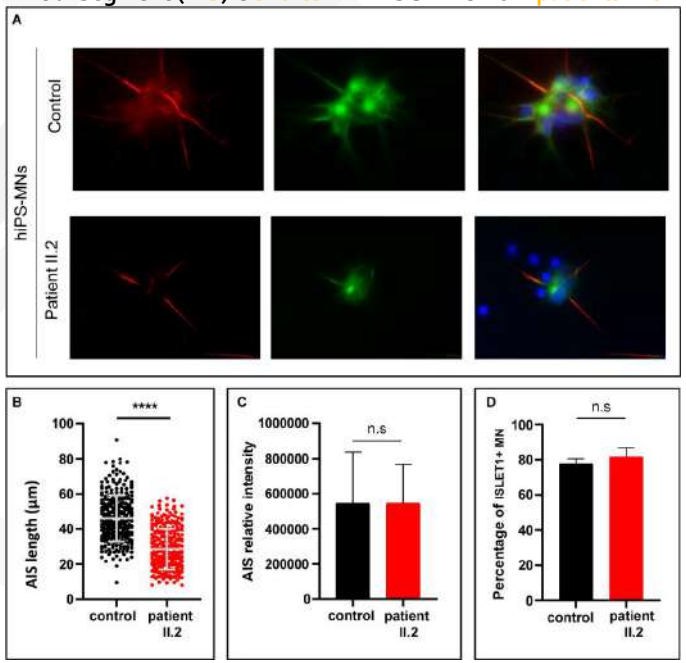
hiPSC-MNs from patient II.2 with VRK1 mutations (>DIV30)



2. hiPSC-MNs from patient II.2 display altered AP waveform accompanied with a decrease or peak Na+ currents



3. Axonal Initial Segment (AIS) is shorter in hiPSC-MNs from patients with mutated VRK1



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