

Nuclear mechanical collapse of Purkinje neurons in Ataxia-telangiectasia

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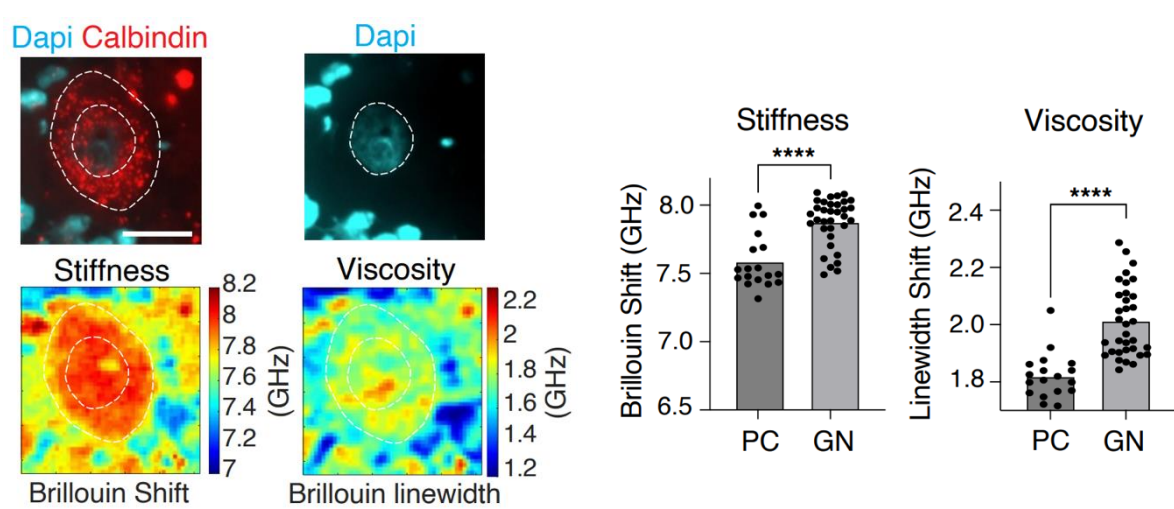
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Introduction

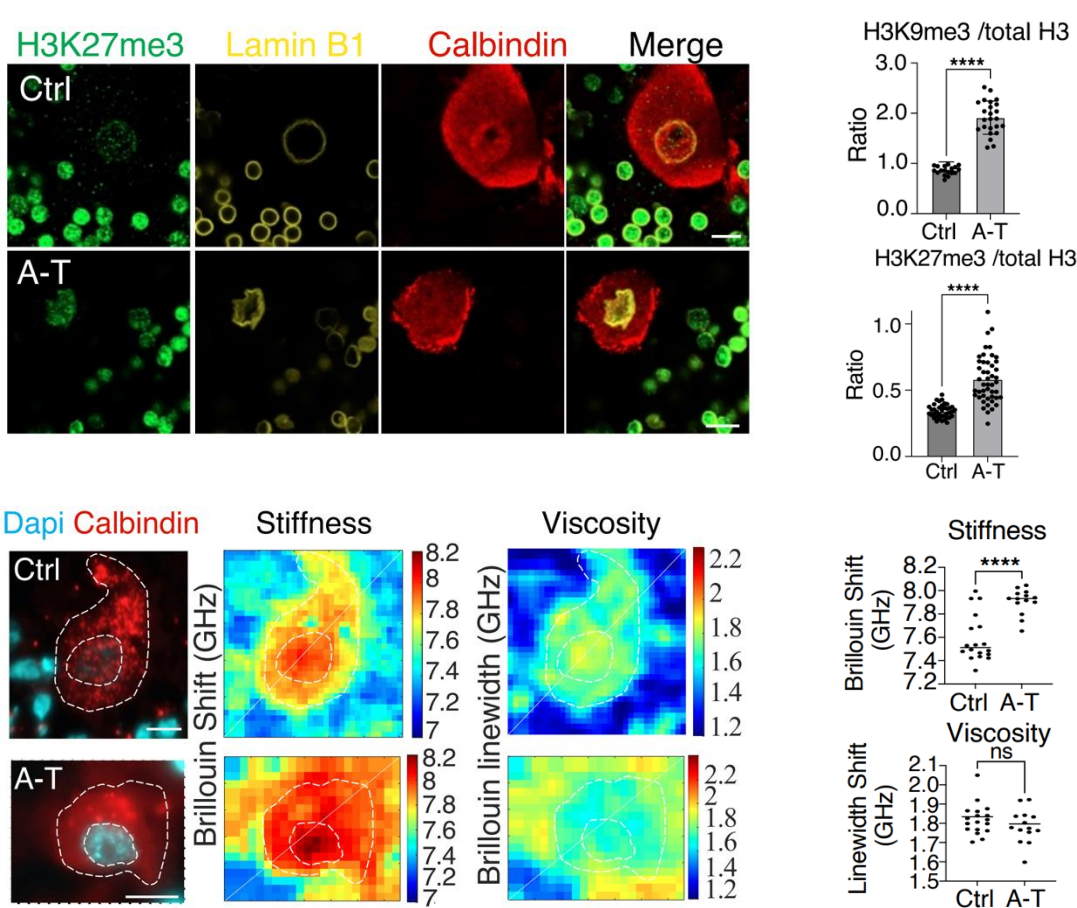
- The Neurodegeneration Paradox in A-T:** Ataxia-Telangiectasia (A-T) is a progressive neurodegenerative disorder caused by inactivating mutations in the ATM kinase. While ATM is classically studied for its role in the DNA Damage Response of proliferating cells, A-T patients suffer from the selective, postnatal loss of non-proliferating cerebellar Purkinje cells (PCs) through mechanisms that remain poorly understood.
- The Cerebellum as a Soft Tissue:** The brain is one of the softest tissues in the body, and the cerebellum is its most mechanically compliant region. To sustain high metabolic and firing rates, healthy human PCs exhibit unique biophysical properties, possessing uniquely large, soft, and euchromatic nuclei.
- ATM as a Mechanical Sensor:** Beyond its role in DNA repair, ATM is capable of sensing mechanical deformations. It coordinates cytoskeletal and chromatin remodelling (via KAP1 phosphorylation) to maintain nuclear resilience against mechanical stress.
- Hypothesis:** We hypothesize that the intrinsic viscoelastic softness and open chromatin landscape of PCs render them uniquely vulnerable to mechanical stress upon the loss of ATM, characterizing A-T as a novel "mechano-disease".

Results

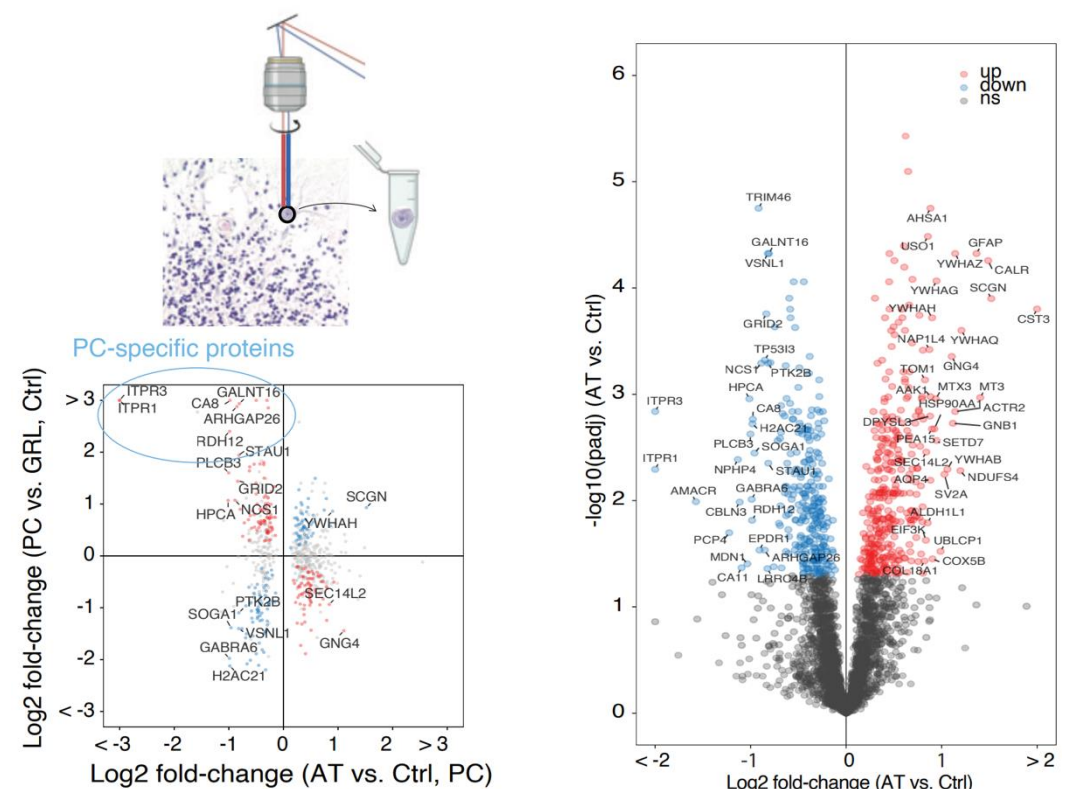
1. Purkinje cells are mechanically soft with large euchromatic nuclei.



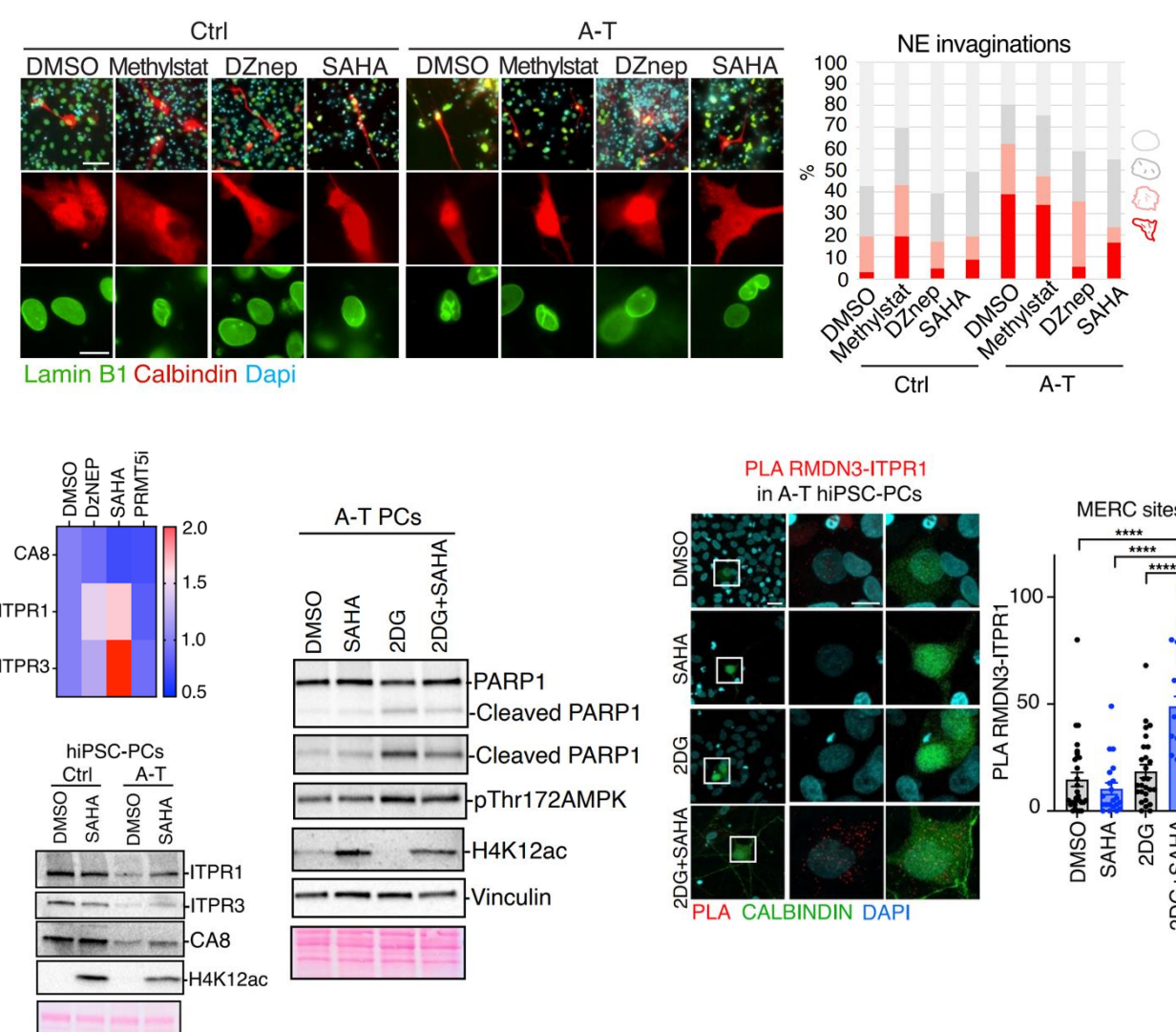
2. A-T Purkinje cells become heterochromatic, hyper-stiff, and develop nuclear envelope invaginations



3. LCM proteomics reveals calcium channel depletion and epigenetic remodelling in A-T Purkinje cells



4. Pharmacological inhibition of heterochromatin rescues nuclear defects, calcium signalling protein expression, and glycolytic stress sensitivity



Model

