

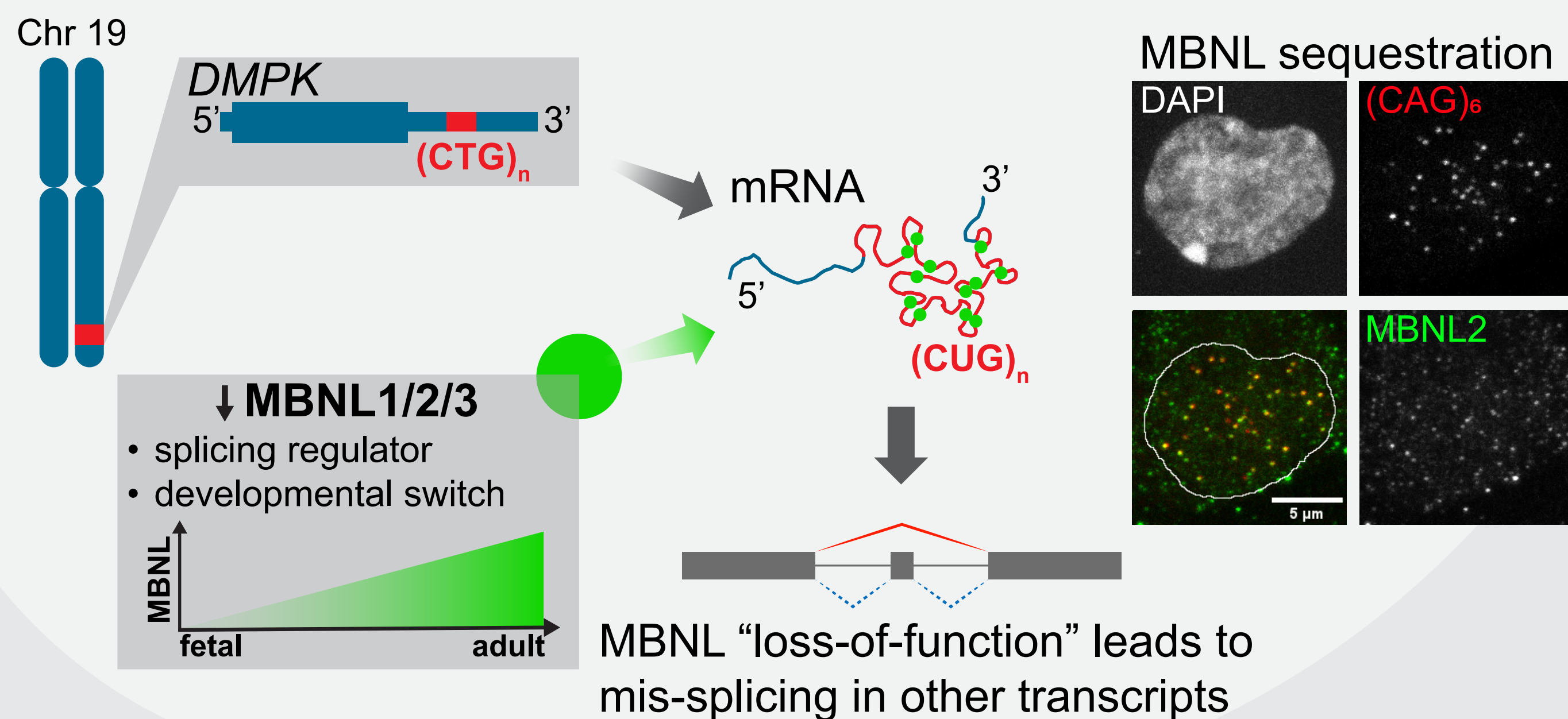
Patient-derived iPSC models suggest astrocytic involvement in DM1 neuropathology

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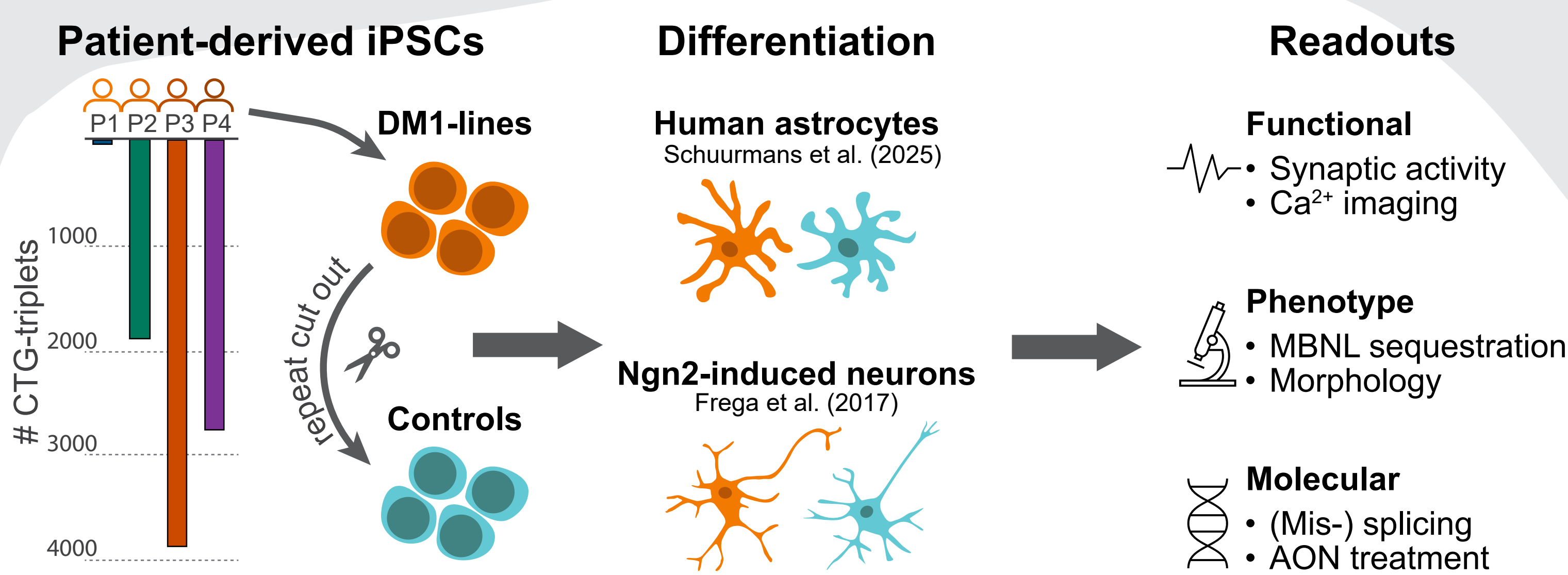
Introduction

Myotonic dystrophy type 1 (DM1) is caused by a CTG-repeat expansion in the *DMPK* gene, producing toxic RNA that sequesters MBNL proteins and disrupts RNA splicing. In addition to muscular symptoms, DM1 causes cognitive impairments, suggesting central nervous system involvement. We model these effects using patient-derived iPSC-derived neurons (iNeurons) and astrocytes (hAstrocytes).



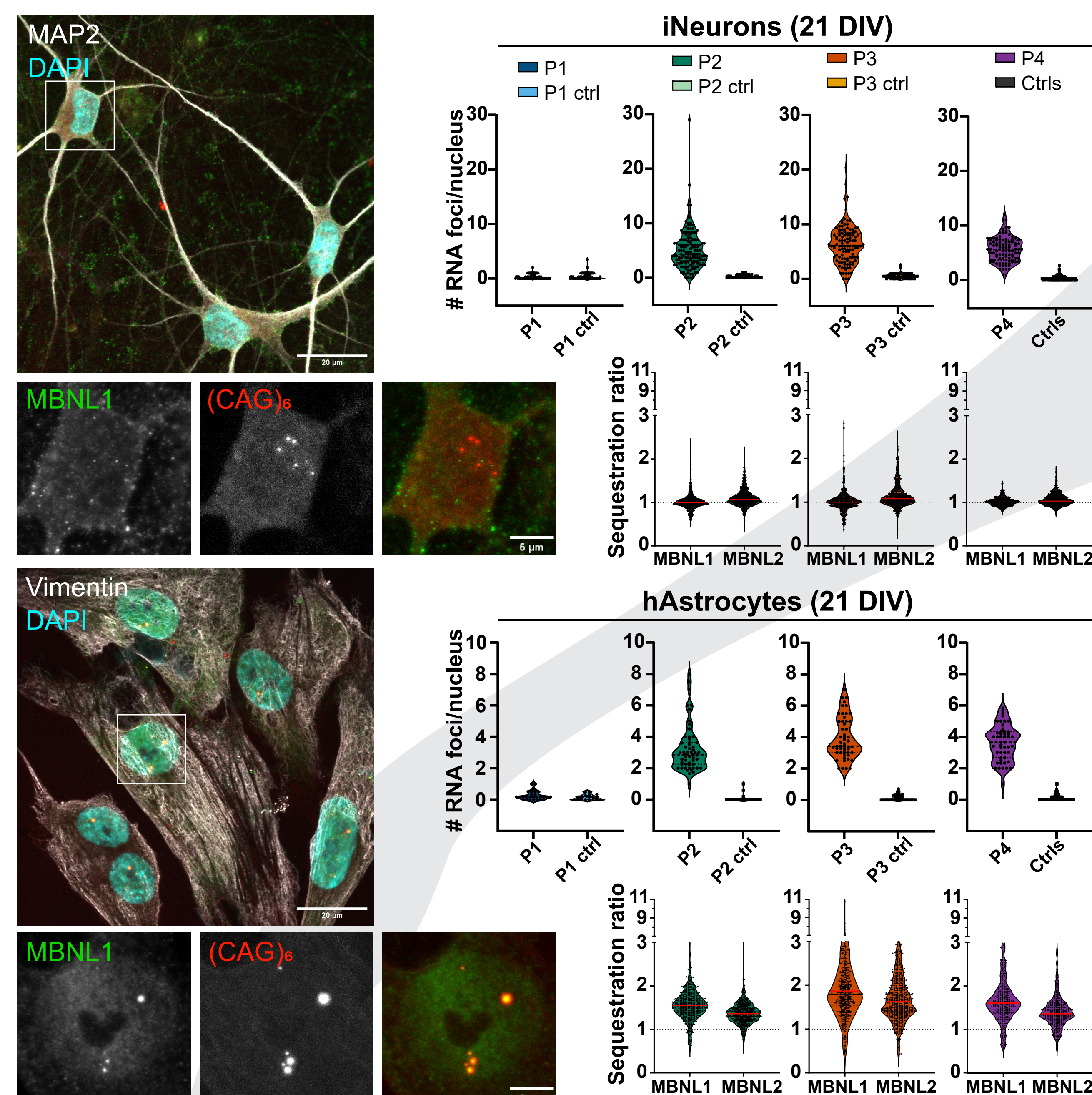
AIM: Which {Cell-Types, Transcripts, Functions} are affected in the DM1 brain?

Methods

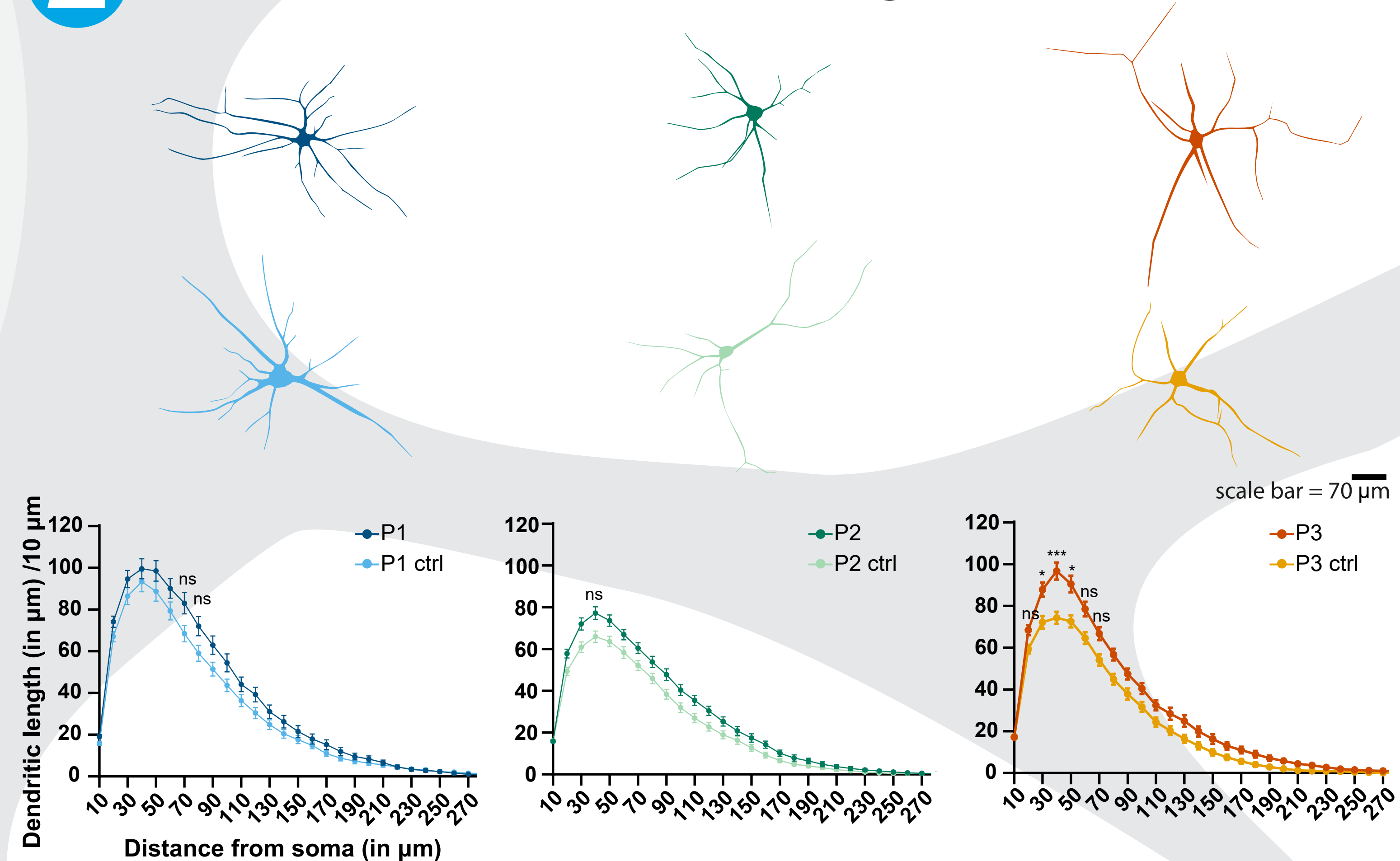


Results

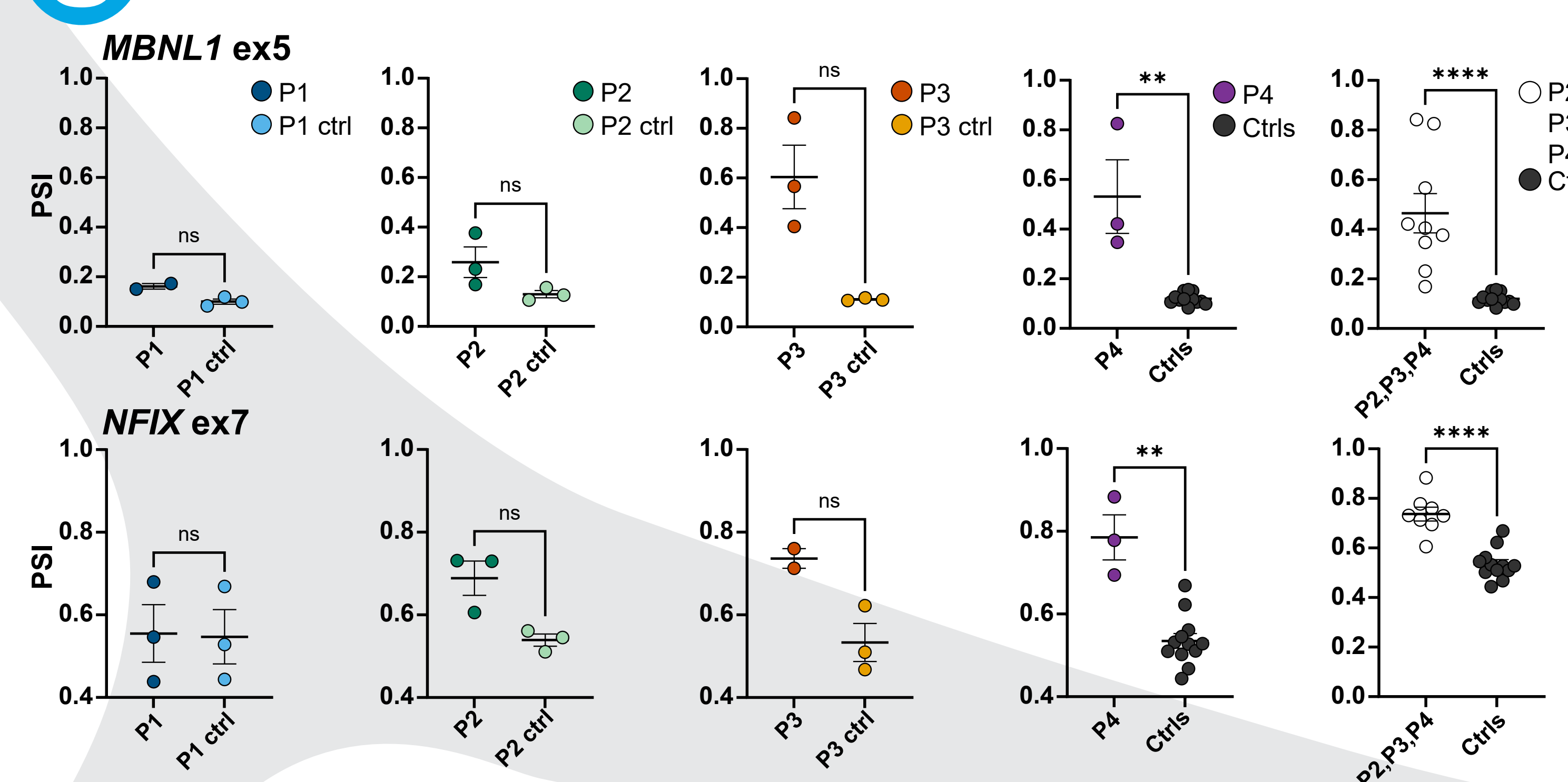
1 iNeurons show more repeat-foci but hAstrocytes have more MBNL sequestration



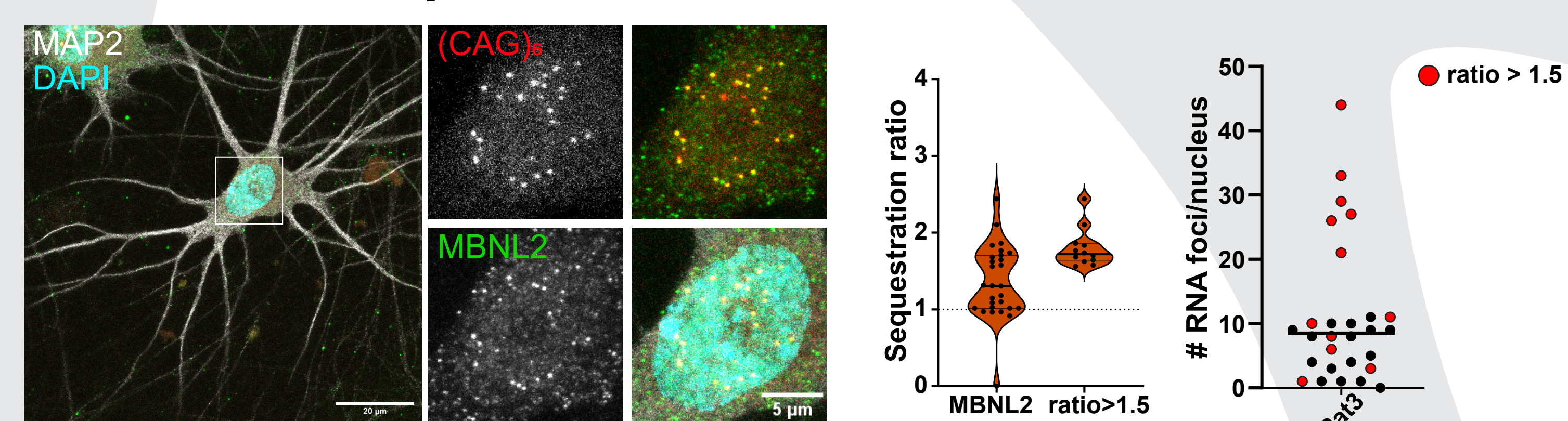
2 iNeurons show minor morphological differences



3 Differentially spliced exons in hAstrocytes



4 A subpopulation of iNeurons shows MBNL2 sequestration



Conclusions

➤ **Astrocytes may represent a key contributor to CNS involvement in DM1**
Despite lower *DMPK* expression, astrocytes appear more affected by the expanded CTG repeat than iNeurons, showing pronounced MBNL sequestration and mis-splicing.

➤ **Neuronal vulnerability may be heterogeneous and cell-state dependent**
Bulk iNeuron analyses revealed no clear morphological defects. Notably, only a subpopulation showed MBNL2 sequestration, highlighting potential neuronal heterogeneity in DM1.

➤ **Astrocyte–neuron interaction may be key to DM1 brain pathology**
Astrocyte dysfunction may indirectly impair neuronal function in the brain, making astrocyte–neuron co-culture models a key next step.

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