

Electrophysiological characteristics of human induced pluripotent stem cell-derived neurons with *CACNA1A* variants

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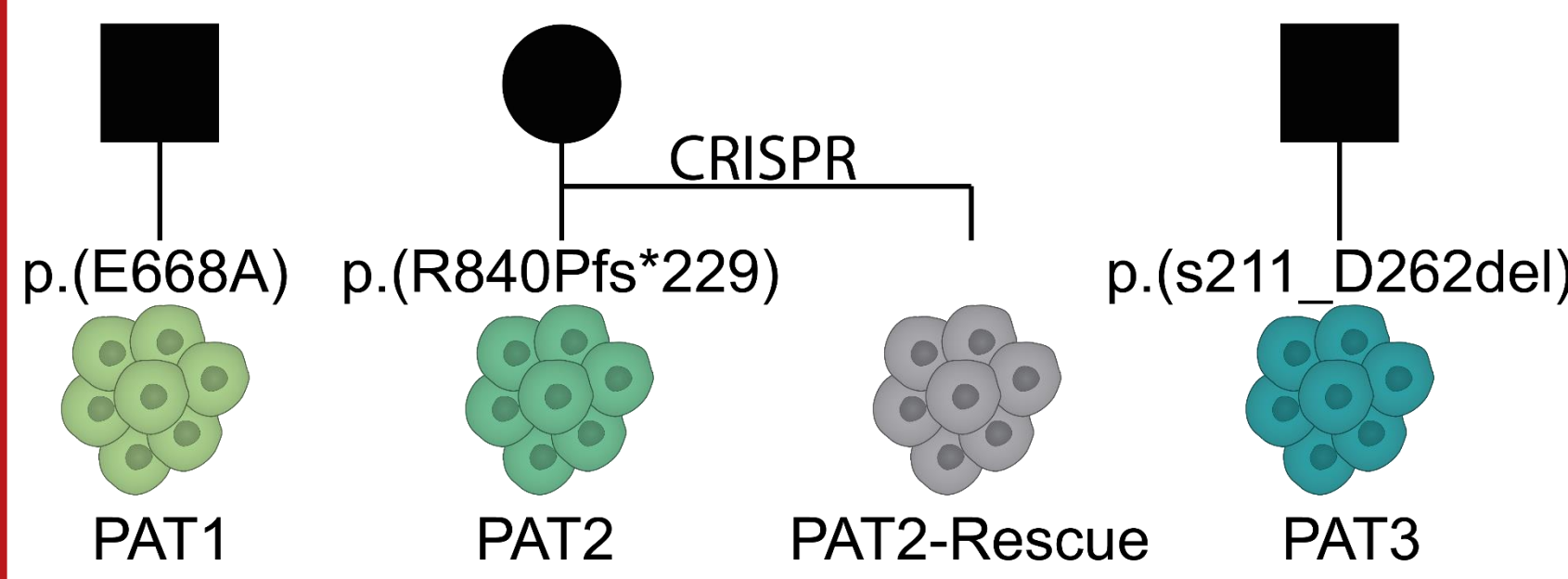
Introduction

CACNA1A loss-of-function variants cause episodic ataxia type 2 (EA2). *CACNA1A* encodes $\text{Ca}_v2.1$, the pore-forming subunit of the voltage-gated P/Q type Ca^{2+} channel, which is important for synaptic vesicle release.

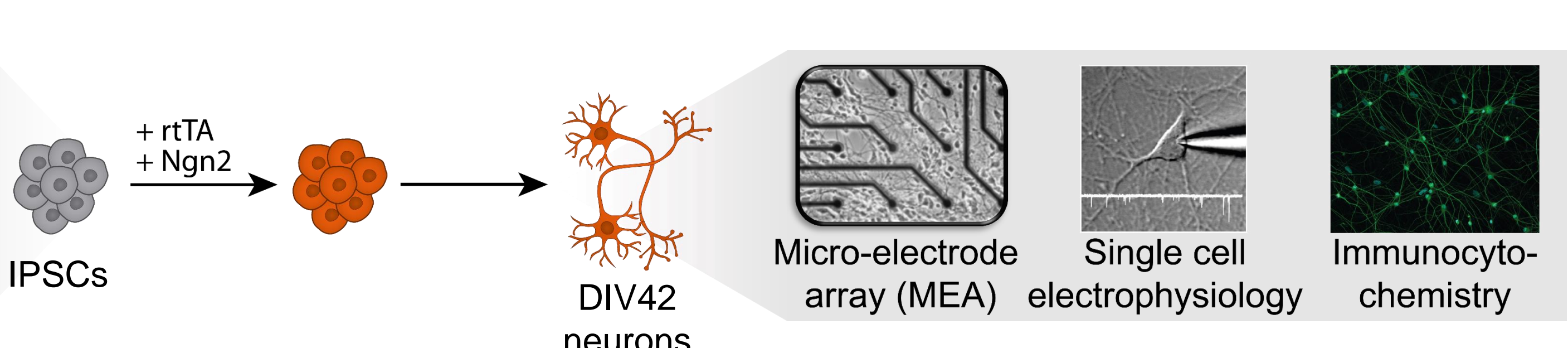
We aim to characterize the effects of *CACNA1A* haploinsufficiency on the neuronal network by examining induced pluripotent stem cell-derived excitatory neurons with multi-level functional analyses.

Strategy

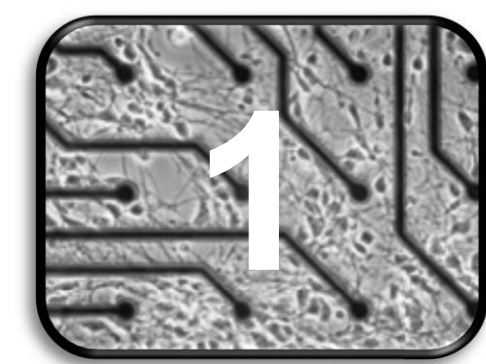
A. Cell lines generated for this study¹



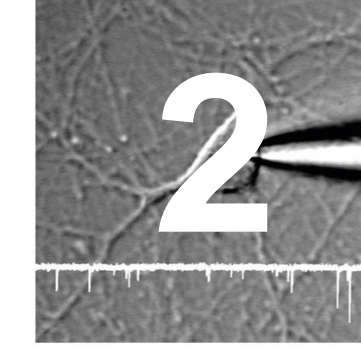
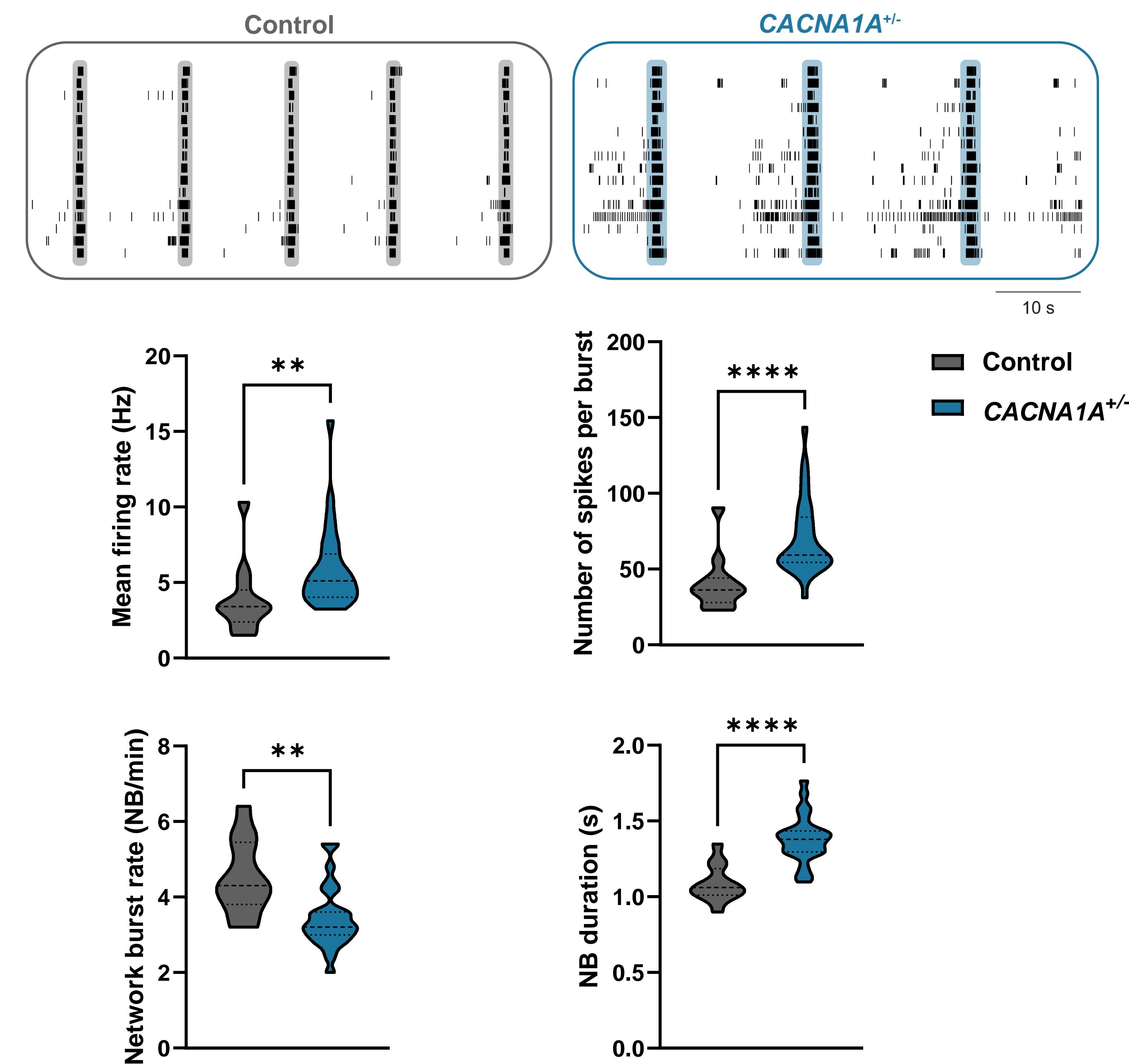
B. Experimental Design²



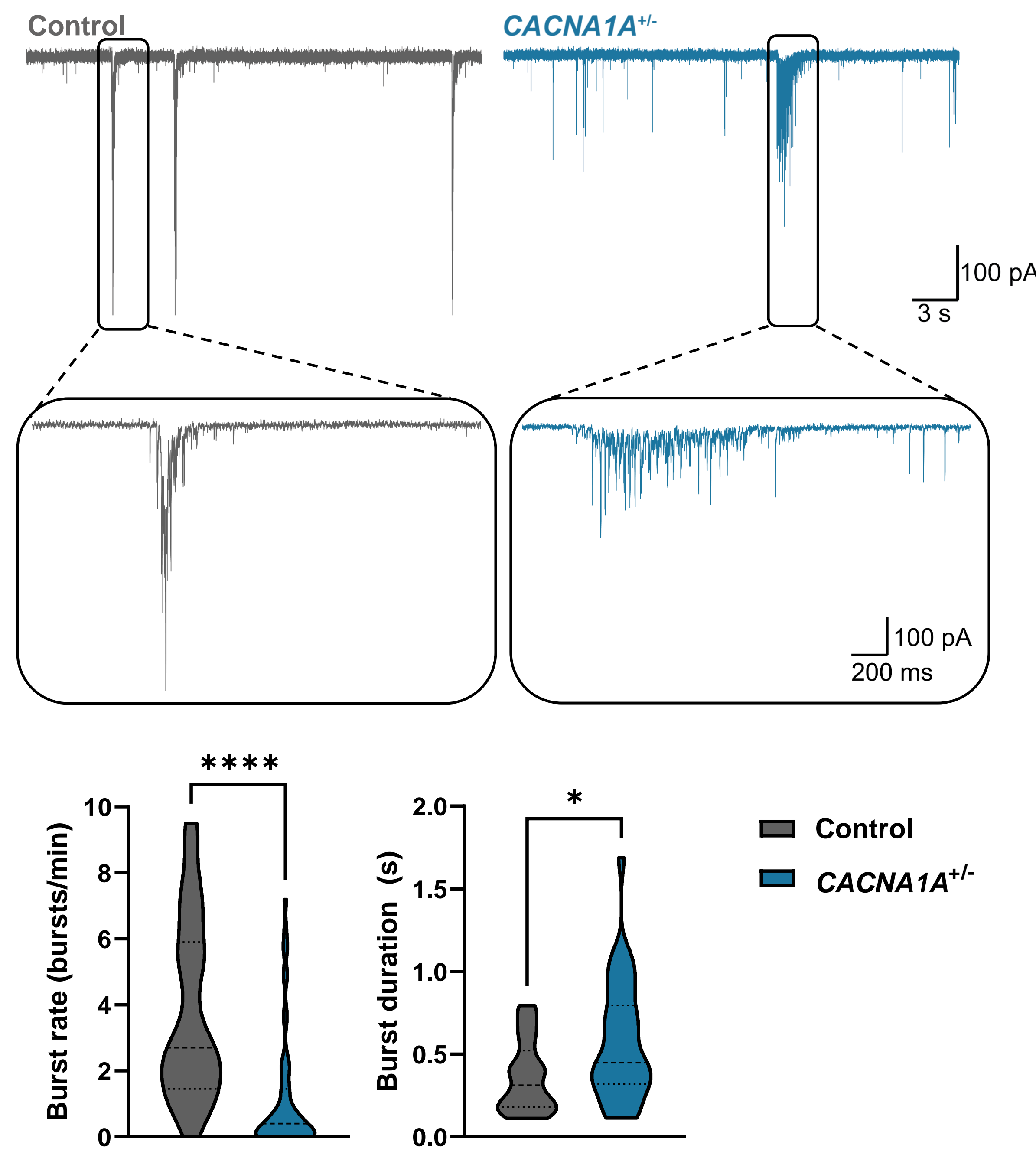
Results



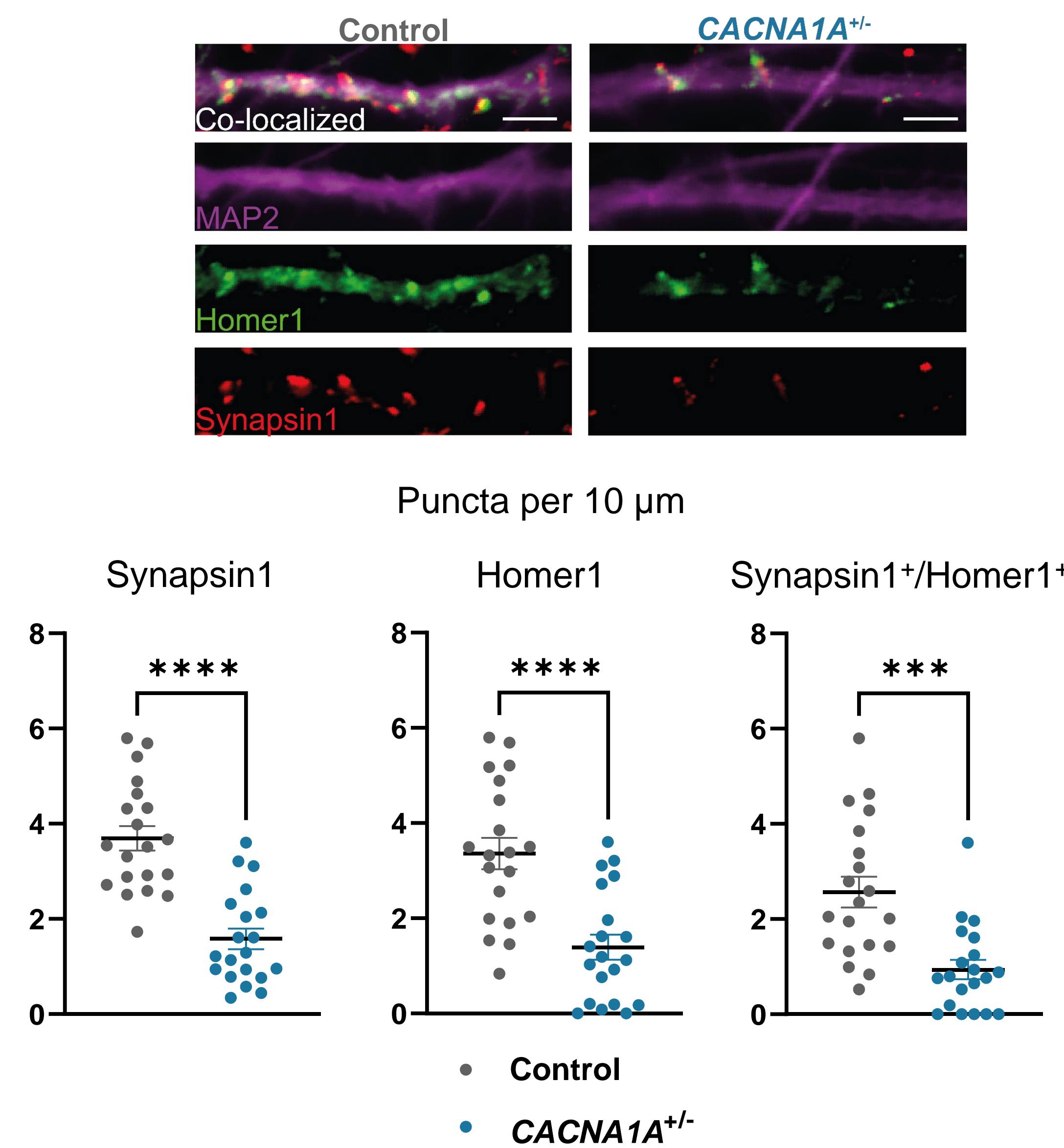
CACNA1A-deficient neurons show an increased firing rate and spiking within bursts, and a reduction in network burst rate



CACNA1A-deficient neurons show a reduced burst rate and increased burst duration at single cell level



CACNA1A-deficient neurons show less functional synapses



Note: in all figures, the two independent *CACNA1A*^{+/-} cell lines are combined.

Conclusion

We show an **altered network activity** of *CACNA1A*-deficient neurons with a reduced network burst rate and an increased network burst duration. These results are **replicated in single cell measurements**. Together with a **reduction of functional synapses**, we show a reduction of **integration** of single cells into the network. In our next steps, we will proceed with the patient cell lines. Ultimately, the altered network activity might offer opportunities for **diagnostic and therapeutic pipelines** in *CACNA1A*.

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