Effects of KCNT1 mutations on adult neurogenesis

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Introduction

- Adult neurogenesis important for learning and memory is disrupted by epileptic seizures (Ming and Song, 2011, Danzer, 2012).
- Effect of malignant migrating partial seizures of infancy (MMPSI) caused by KCNT1 mutations on neurogenesis is not known.
- The experiment aimed to address this by analysing changes to migration and proliferation of neurons and glia in sub-dentate gyrus (SDG).

Methods

- Control and KCNT1-R409Q mice brain slices were stained with fluorescent antibodies against markers for proliferation (EdU), neuronal stem cells (Sox2), new-born neurons (HuC/D), astrocytes (GFAP), and oligodendrocytes (Olig2).
- Images were captured with fluorescence microscope and analysed with ImageJ for cell counting.
- Co-localisation between EdU and a cell specific maker was used as a measure of specific cell proliferation.

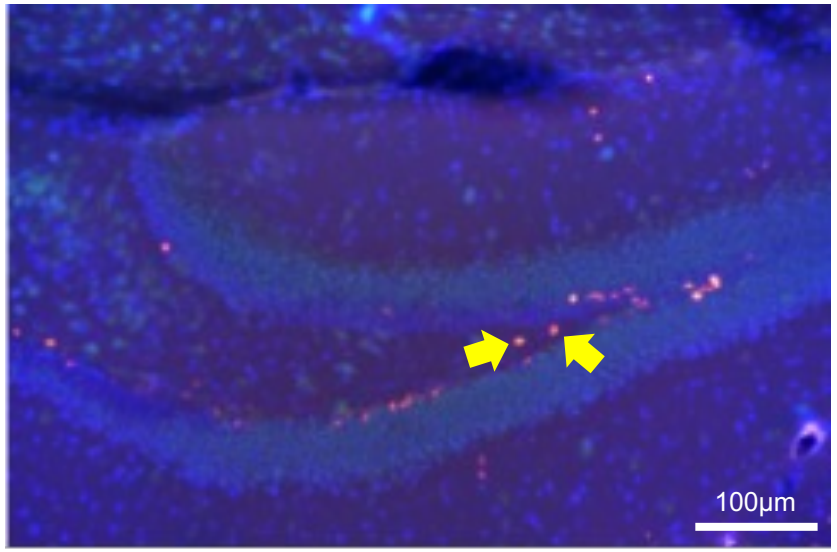

Fig. 1. Immunofluorescent image showing colocalization of EdU and HuC/D (red) in sub-dentate gyrus. Prescence of new-born neurons in hilar region outside of granular layer is highlighted with yellow arrows.

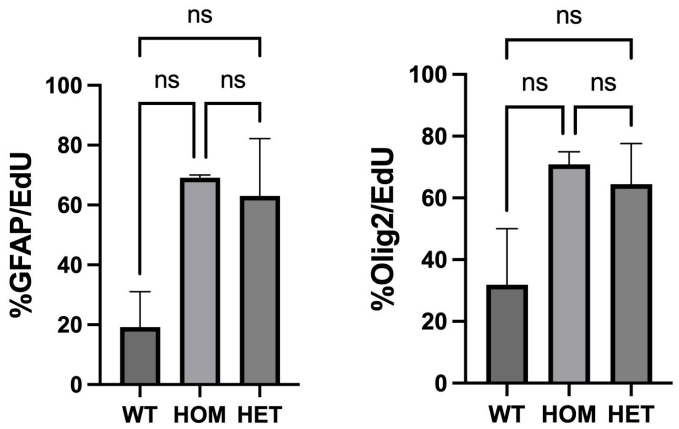

Fig. 2. Proliferation of astrocytes (GFAP) and oligodendrocytes (Olig2) between wild-type mice, homozygous mutant and heterozygous mutant mice. NS: Not significant.

Results

- Difference in proliferation of neuronal stem cells and new-born neurons not significant between genotypes.
- Abnormal presence of new-born neurons detected in hilar region (Fig.1).
- Mutant mice show higher proliferation of astrocytes and oligodendrocytes (Fig.2).
- Although not significant, this was deemed as type-II statistical error due to extremely low sample size (n=38 for neurons, n=6 for astrocytes, n=8 for oligodendrocytes).

Conclusions

- KCNT1 mutation did not affect rate of neurogenesis but caused abnormal migration of new-born neurons into hilar region, leading to aberrant integration into local neuronal circuits.
- KCNT1 mutation may have increased proliferation of astrocytes and oligodendrocytes.
- These changes may underly pathology of MMPSI.
- Further experiments required to investigate how aberrant integration and increased in glia affect normal function.

References

Danzer., 2012. *Exp Neurol,* 233, 22-32.
Ming and Song., 2011. *Neuron,* 70, 687-702.