# Effects of Lamotrigine on Seizures and Respiration in a Mouse Model of Dravet Syndrome

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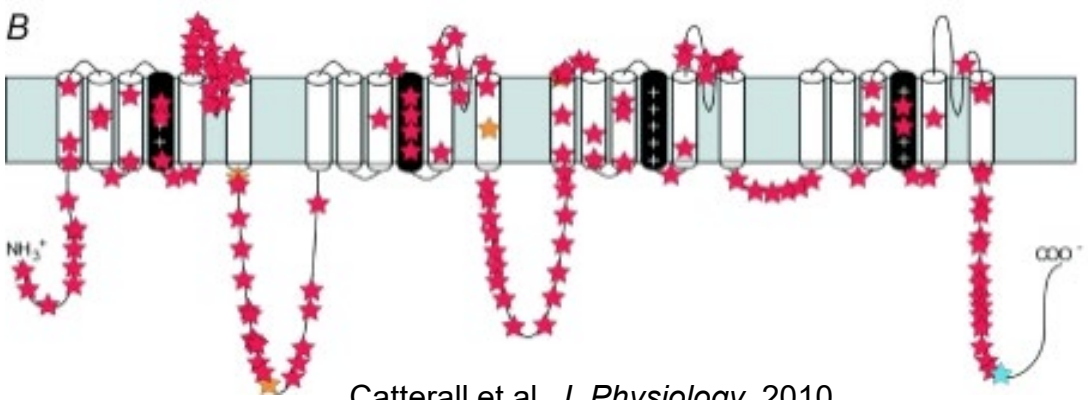
# What is Dravet Syndrome (DS)?

- Genetic epilepsy beginning in infancy that continues throughout adulthood.
- Caused by a loss-of-function mutation in the SCN1A gene, creating the incomplete $Na_V1.1$ sodium channel.
- Affects the excitement of GABAergic interneurons in the brain.
- Symptoms begin as early as one year of birth and the lifelong consequences include severe seizures, ataxia, cognitive impairment, and risk of sudden death (SUDEP).




Catterall et al. *J. Physiology*, 2010

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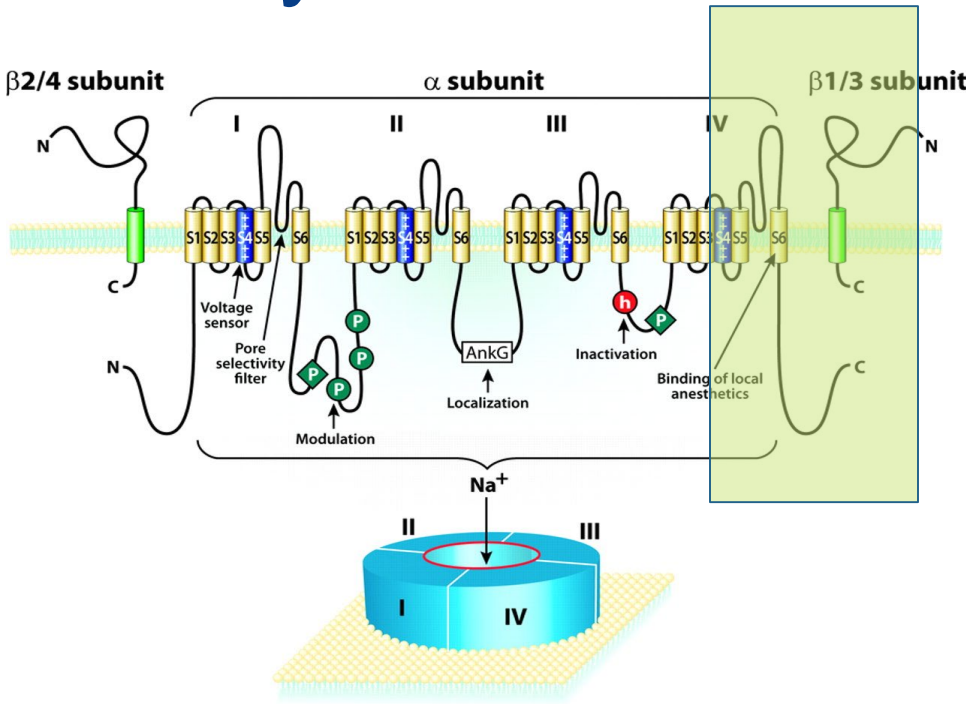
# Mouse Model of Dravet Syndrome

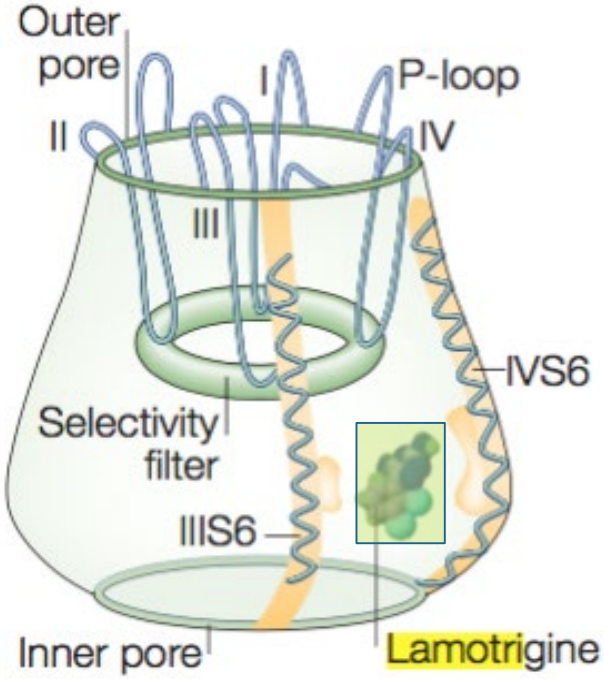
- Generated by deleting the last coding exon of the SCN1A gene.
- Genotyping
- The heterozygous *Scn1a* mice experience symptoms of Dravet Syndrome early on.
  - Seizure
  - Ataxia
  - Also, SUDEP




Benarroch, *Neurology*, 2007

# Lamotrigine (LTG)

- LTG is a well established anti-epileptic drug.
  - Often used in patients with severe epilepsy, especially those with both focal and generalized onset seizures
  - It mainly acts through blocking sodium channels
- DS patients carry a loss of function mutation in the sodium channel gene
  - Some investigators have postulated that having the pharmacological blockade of $Na_V$ channels on top of genetic lesion of $Na_V$ channels in DS is what lead to exacerbation of epilepsy symptoms in DS
  - This hypothesis has never been tested




Rogawski et al., 2004 Fig 2

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# SUDEP and LTG

- Sudden Unexpected Death in Epilepsy is a devastating outcome of epilepsy
- Previous studies have determined SUDEP to be associated with an abnormal cardiac activity and respiration
- Clinical observations have reported that LTG aggravates epilepsy symptoms in DS patients
- In addition, recent studies indicated that LTG may constitute a risk factor for SUDEP
- The mechanism of the adverse effects of LTG is not completely understood.

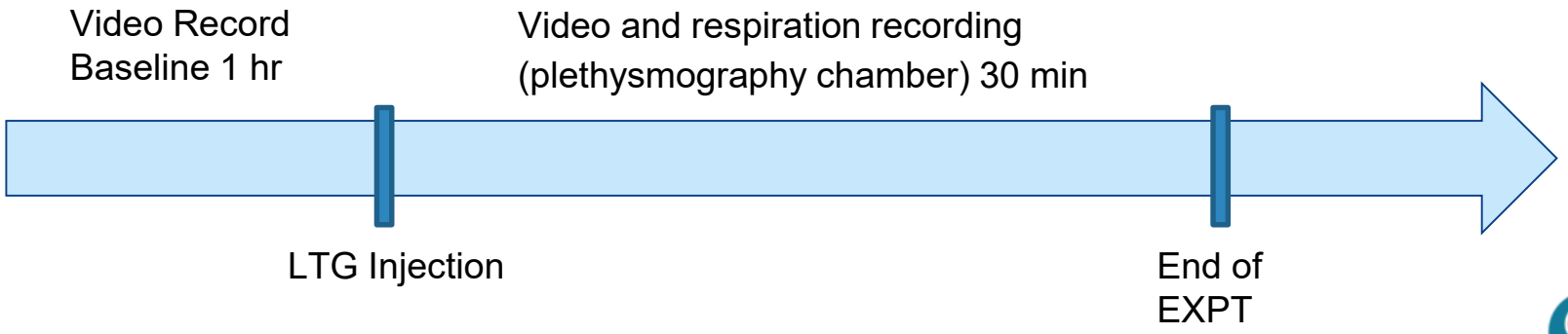
# Aims:

- Investigate:
  - 1) Does Lamotrigine exacerbate the seizure phenotype in Dravet Syndrome mice?
  - 2) Does Lamotrigine increase risk for Sudden Death in Dravet Syndrome mice?

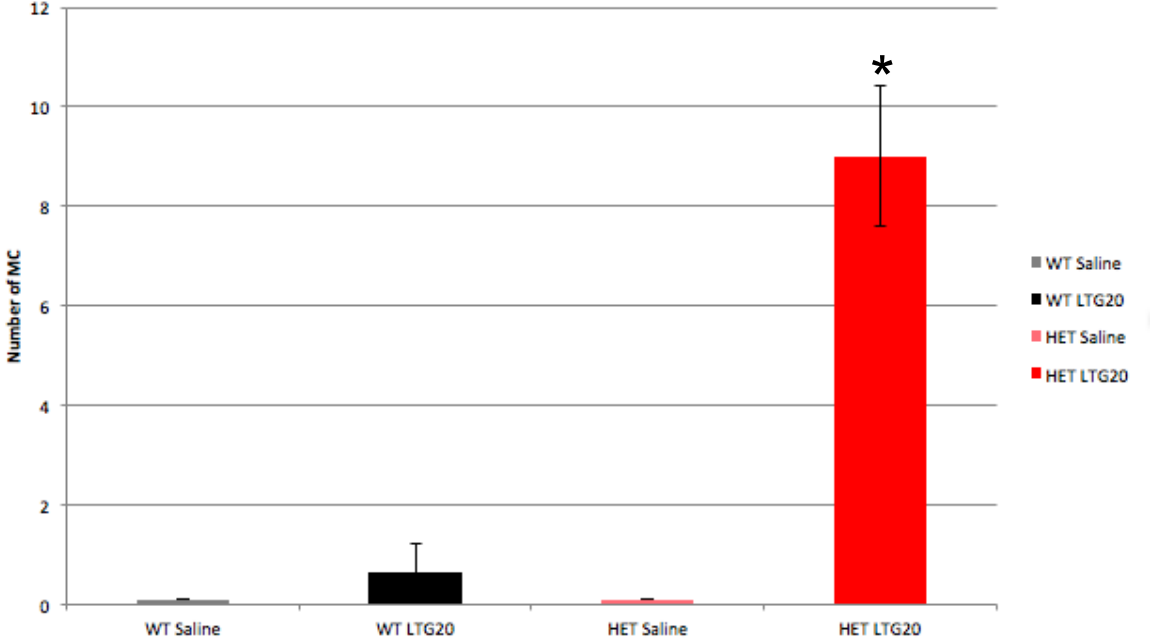
- Hypothesis: The presence of the *Scn1a* mutation confers an increased risk to Lamotrigine-related exaggeration of seizures and SUDEP phenotypes in Dravet Syndrome mice.

# Experimental Methods

- Conduct behavioral assay to test the susceptibility of the mouse model to Lamotrigine.
  - Tested mice at 20 mg/kg dose of Lamotrigine and observe for myoclonic seizures for 30 minutes.
  - Tested mice at 40 mg/kg dose of Lamotrigine, similar procedure as above.
  - Conducted plethysmography experiment for 30 minutes, while observing for myoclonic seizures.



# Results: Effect of different doses of LTG or myoclonic seizures




- LTG20
  - WT mice (n=3)
  - HET mice (n=3)

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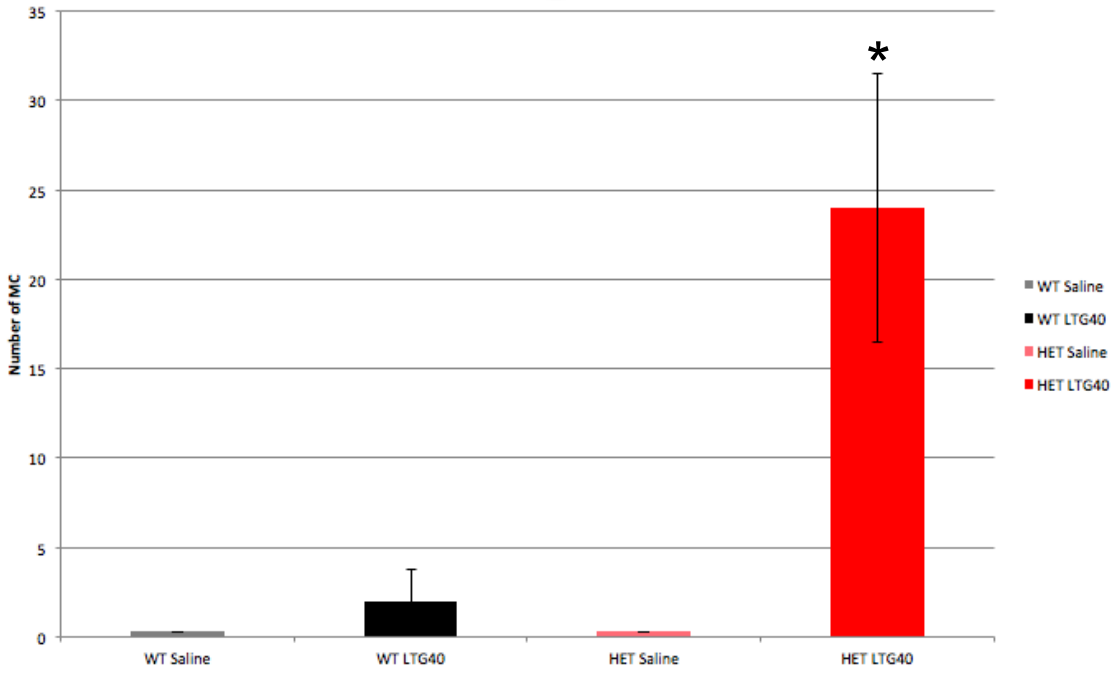
# Results: Effect of different doses of LTG of myoclonic seizures (cont.)

- LTG40
  - WT mice (n=3)
  - HET mice (n=3)
- Drug-dose dependent?

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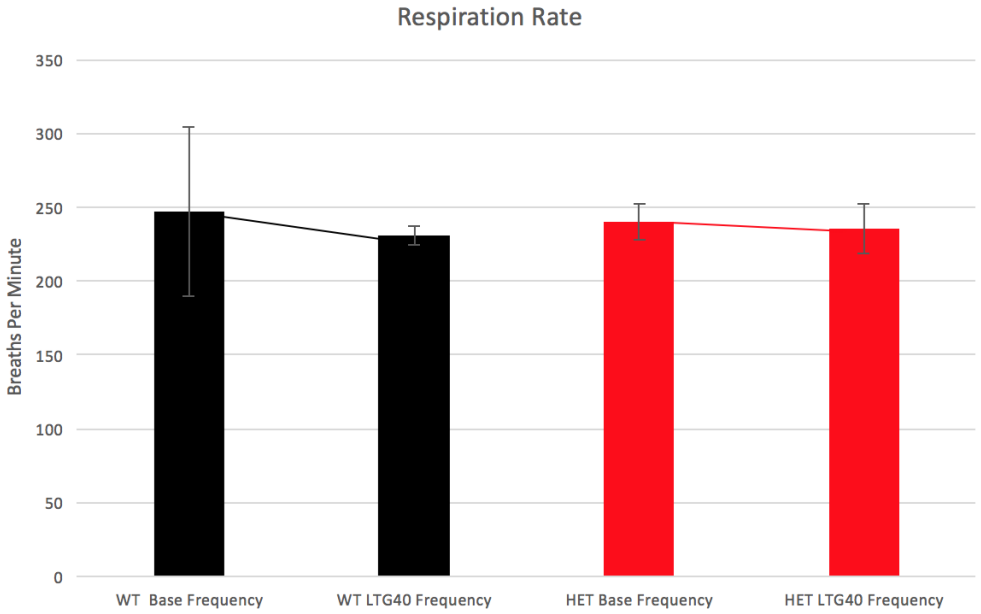
# Results: Effect of different dosage of LTG o respiration

- Lamotrigine decreased respiration rate in both WTs and mutants
- Goal: Investigate if there's an abnormal respiratory function that's associated with SUDEP

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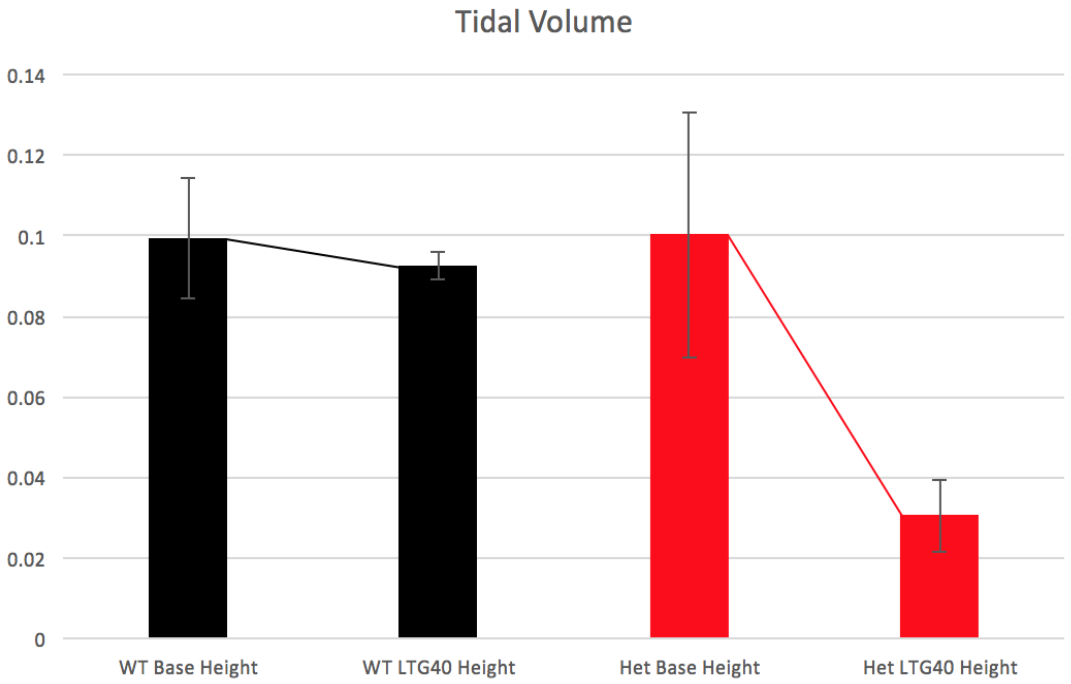
# Tidal Volume

- With injection of LTG, Tidal volume decreased significantly in the Het *Scn1a*
- Het *Scn1a* mice tidal volume decreased by 36%
- WT *Scn1a* tidal volume decreased by 7%

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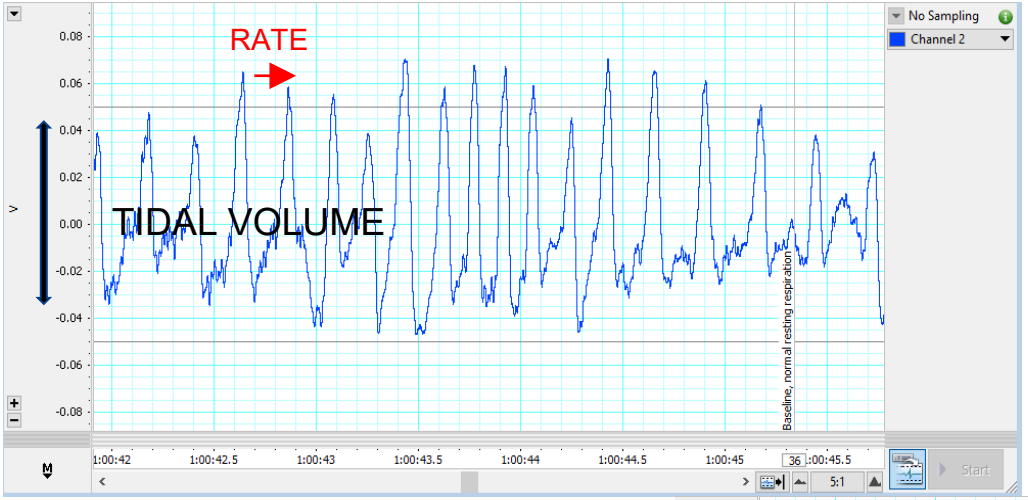
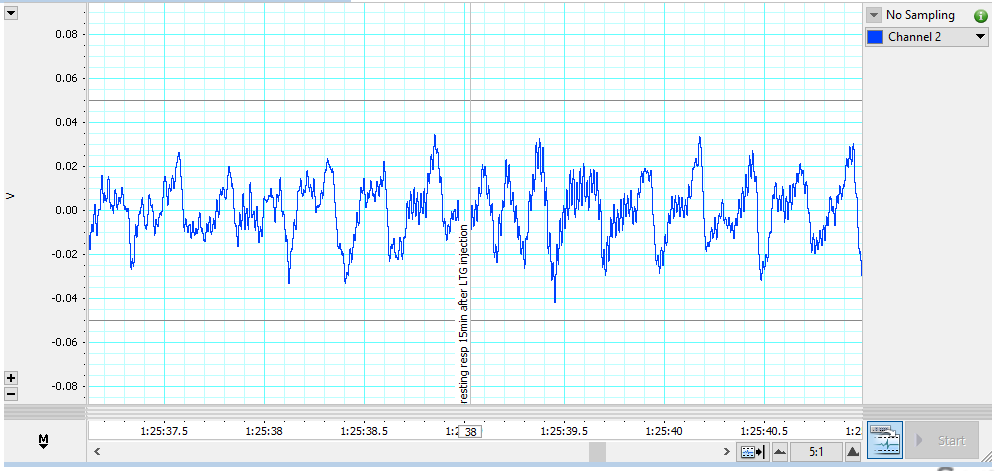



← Baseline Normal Resting Respiration

Minute Ventilation= RATE X TIDAL VOLUME

Resting Respiration 15 min after LTG Injection →

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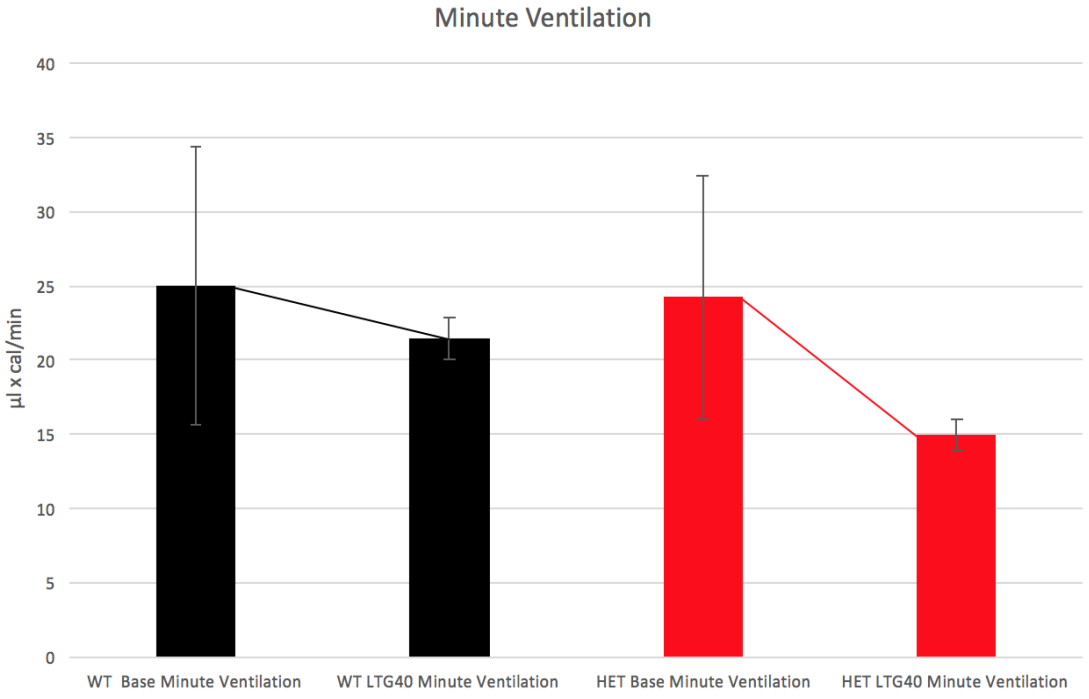
# Minute Ventilation

- Minute ventilation decreases after lamotrigine injection for both WT and Het
- Lamotrigine appears to have a big effect on the mutants
  - With injection of LTG, the minute ventilation decreased by 38.09% on the HET mice
  - WT decreased by 14.37%

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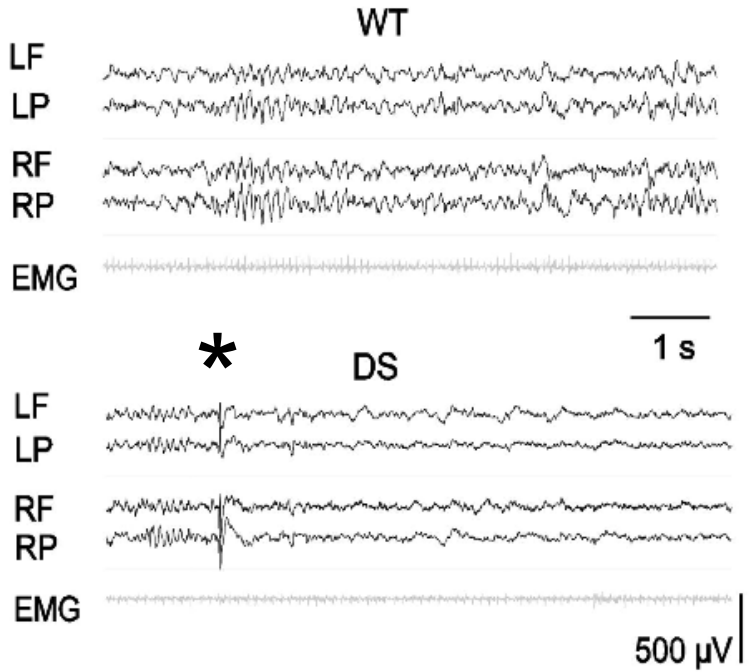
# Conclusions

- We have demonstrated that Lamotrigine does exacerbate epilepsy phenotype in DS mice.
  - 35.7% increase in myoclonic seizures

- Lamotrigine also suppresses respiration in DS mice.
  - 38.09% decrease in minute ventilation.
  - This may be linked to a LTG-induced increase of susceptibility to SUDEP.

# Future Directions

- Continue project to include analysis of single cell and slice electrophysiology to provide further information about the mechanism of Lamotrigine at a cellular and network level.
- Conduct EEG to determine abnormal brain activity caused by LTG.
  - This may be myoclonic seizures and interictal/ictal spikes with or without movement manifestation




Kalume et al., 2016 Fig 4

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