



A novel strategy for therapeutic intervention to lissencephaly using calpain inhibitors

Outline

Lissencephaly is a devastating developmental disorder due to defective neuronal migration. The mutated gene LIS1 is a regulatory molecule of cytoplasmic dynein. LIS1 has a short half-life by calpain dependent protein degradation. We have devised a novel strategy for lissencephaly using calpain inhibitors. Currently, we are investigating therapeutic efficiency of calpain inhibitors using LIS1 mutant mice as a model for lissencephaly.

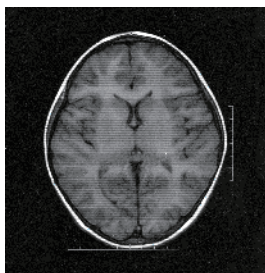
Expected Outcome

An effective therapeutic intervention for lissencephaly has not been established. Our previous study indicates that calpain inhibitors will become a beneficial approach for lissencephaly through augmentation of LIS1 protein. In addition, our strategy may be applicable to other genetic diseases due to haploinsufficiency.

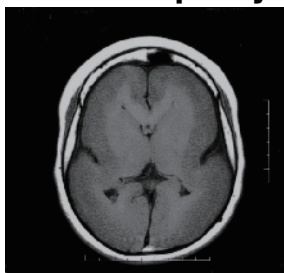
Lissencephaly and LIS1

MRI image

Normal



Lissencephaly

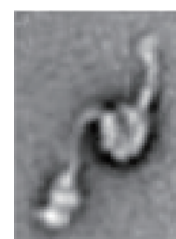
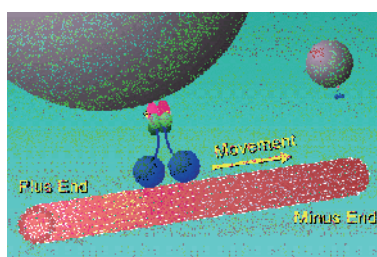


1. Lack of brain folding due to defective neuronal migration
2. Severe mental retardation, seizure
3. Morbidity
One/15,000 new born
4. **60%** of lissencephaly is due to hemizygous mutation of Pafah1b1(LIS1).

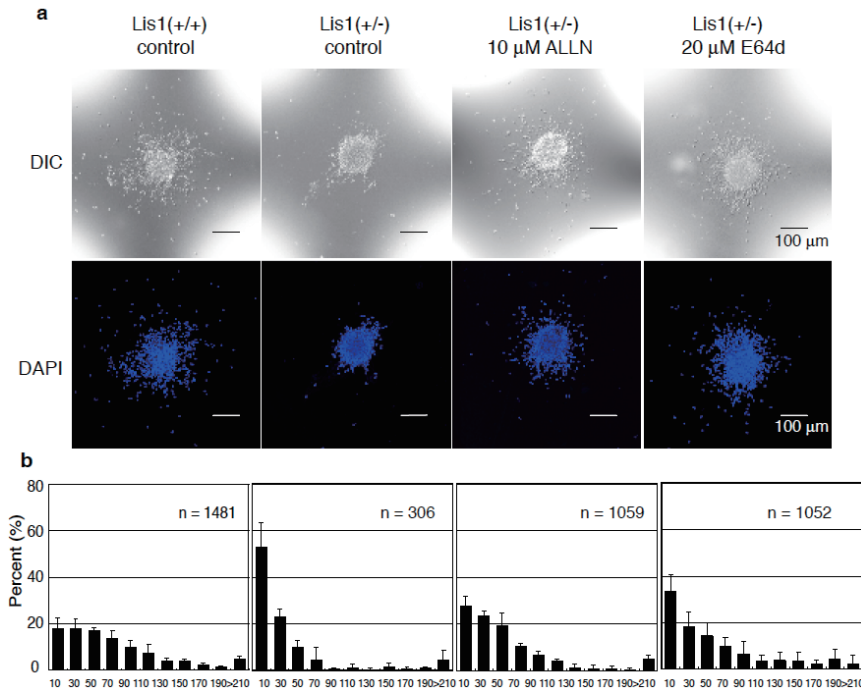
LIS1

Pac1(Yeast), NudF(Aspergillus), D-Lis1(Drosophila)

LIS1 is essential for anterograde transport of cytoplasmic dynein

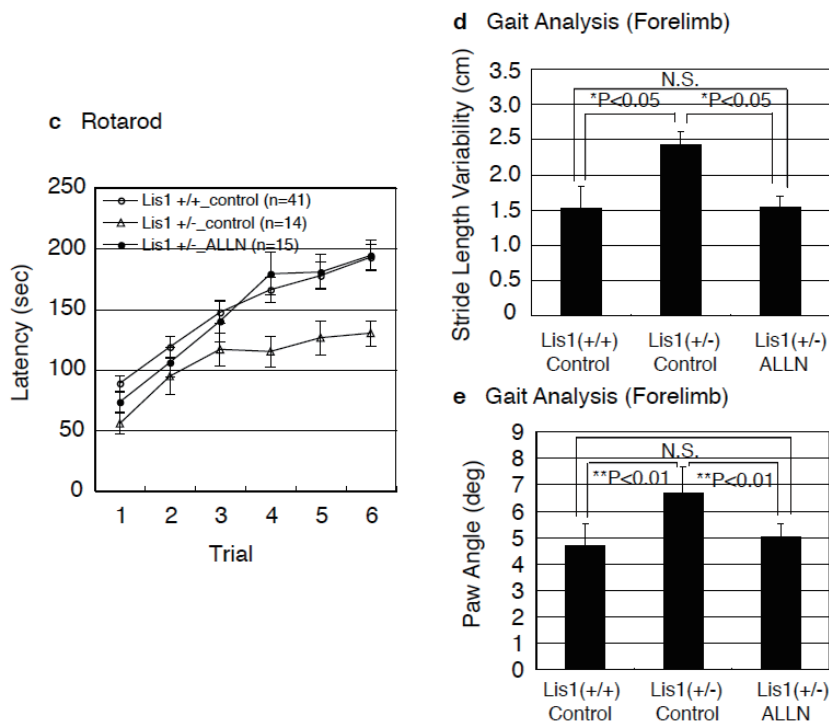


Rescue of defective neuronal migration by calpain inhibitors



We found that calpain inhibitors efficiently rescued defective neuronal migration in granular neurons isolated from LIS1 mutants.

Rescue of defective behavior by calpain inhibitors



Defective behaviors in LIS1 mutant was rescued by administration of calpain inhibitors.