# Trisomic dosage imbalance exhibits tissue, temporal, and sex specific non-linear genetic expression in a Down syndrome mouse model

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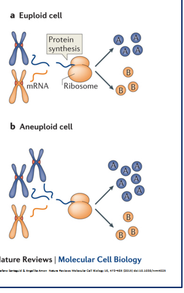
## Background

- Trisomy 21 causes Down syndrome (DS) in humans
- Trisomic gene dosage imbalance causes DS phenotypes
- Three copy as compared to two copy genes expected to be upregulated 1.5 fold in every cell (see right)
- *Dyrk1a* = dosage sensitive gene important in cognitive and skeletal DS phenotypes
- Reducing *Dyrk1a* to normal copy number at conception in otherwise trisomic mice normalizes some DS cognitive and skeletal phenotypes
- Reduction of DYRK1A activity is a therapeutic goal to correct DS phenotypes




## Motivation and Hypothesis

- While trying to normalize DYRK1A protein expression in DS mouse models, we found that DYRK1A expression was not upregulated 1.5-fold as expected at ~2 months in Ts65Dn mice (see right)
- We wanted to normalize DYRK1A expression only when it was upregulated
- Expression levels of trisomic *Dyrk1a* not well known, especially during development
- **We hypothesized that DYRK1A expression is temporally and spatially regulated in DS mouse models**

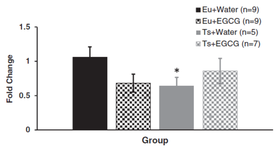
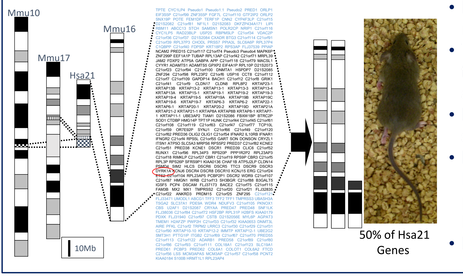



**Fig. 5. Dyrk1a Protein Levels-Cerebellum.** Dyrk1a protein levels in the cerebellum of ~9-week old mice given 6 weeks of treatment with water or EGCG (mean ± SEM). Ts65Dn mice receiving water had significantly less Dyrk1a protein that euploid-water controls (as indicated by the *, genotype × treatment interaction, p = 0.043).

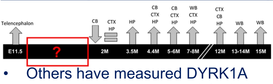
Stringer et. al. *Physiol Behav.* 2017;177:230-241. doi: 10.1016/j.physbeh.2017.05.003. PMID: 28478033

## Ts65Dn DS mouse model

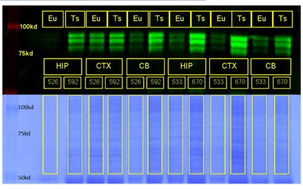



- Most common used DS mouse model
- Three copies of 104 genes that are found on Mmu16 and homologous to Hsa21
- Extra genes on a freely segregating chromosome
- Display cognitive, behavioral, and skeletal, phenotypes similar to humans with DS
- Has three copies of *Dyrk1a*

## Unknown period of DYRK1A expression measured by Western blot



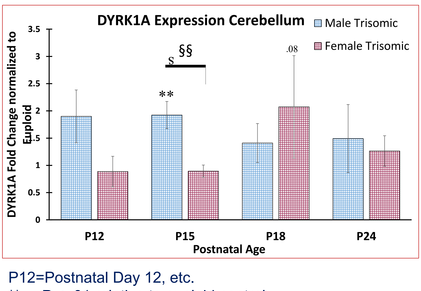

- Others have measured DYRK1A expression in mouse models during different developmental times in different brain regions.
- We measured DYRK1A protein expression of in 3-6 day windows during development in cerebellum (CB), hippocampus (HIP) and cerebral cortex (CTX) of Ts65Dn and control littermate mice




- Top: DYRK1A antibody (M01, clone 7D10, Abnova)
- Bottom: Coomassie-stained membrane (same membrane as above)
- Protein from trisomic and euploid littermates for each brain region loaded in adjacent lanes.

## Temporally, spatially and sex specific DYRK1A expression

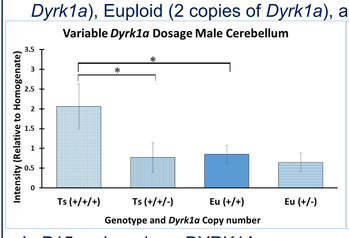
- DYRK1A protein expression in Ts65Dn as compared to normal brains varies during development from 1- to 5-fold, showing dosage level compensation, expression, and amplification of DYRK1A protein varies according to tissue (only cerebellum shown)
- DYRK1A expression varies according to sex—notice the difference in expression at P15 between males and females

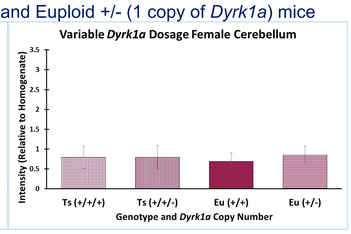



P12=Postnatal Day 12, etc.
** = P < .01 relative to euploid control
§§ = P < .01 difference between sexes

## DYRK1A expression in genetically modified mice

- DYRK1A expression in P15 Ts65Dn (3 copies *Dyrk1a*), Ts65Dn +/+/- (2 copies of *Dyrk1a*), Euploid (2 copies of *Dyrk1a*), and Euploid +/- (1 copy of *Dyrk1a*) mice




- In P15 males where DYRK1A was overexpressed, expression is downregulated with one fewer copy
- In P15 females where DYRK1A was not overexpressed, expression is the same in Ts65Dn, Ts65Dn +/+/-, and Euploid mice

## Conclusions

- Trisomic DYRK1A expression varies during development from the expected 1.5-fold level of expression, some regions have high overexpression, other regions have no overexpression or dosage compensation
- DYRK1A trisomic expression in brain varies according to age, sex, and tissue type
- DYRK1A temporal and tissue specific expression may or may not correlate with gene dosage of *Dyrk1a* found in the tissue
- These data suggest that DYRK1A expression is controlled at the transcriptional, translational, or post-translational level, perhaps by other trisomic genes
- To optimize the effectiveness of potential therapies to reduce activity of DYRK1A, treatments should target the tissue-specific developmental periods of overexpression.

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