Understanding How the Maternal Epigenetic Reprogramming Function of LSD1 Contributes to Inherited Developmental Disease

LSD1 Patients: No Known Cure or Treatment

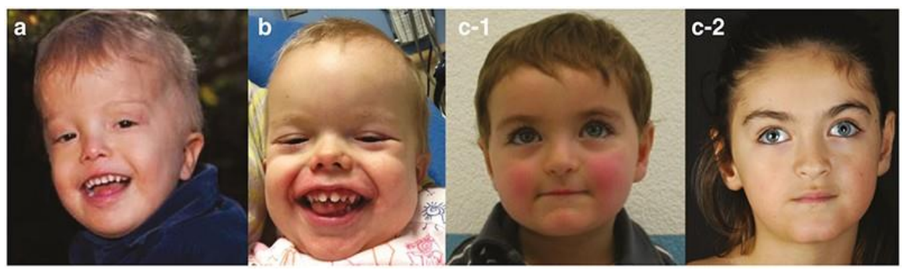

Fig. 1: Patients with LSD1 mutations. *(Chong et. al, Genetics in Medicine, 2015)*

Symptoms: Developmental delay, craniofacial defects, intellectual disability, and repetitive behavior that worsens with age

Current Paradigm

Misexpressed genes during development → **Improper development of nervous system** → **Disease Phenotypes**

How this Research *Challenges* the Current Paradigm

This research suggests:

1) **Some disease phenotypes may be an ongoing functional defect due to the ectopic expression of a subset of germline genes in the nervous system.**
2) **A defect in maternal epigenetic reprogramming contributes to disease phenotypes in the affected progeny.**

Background: Epigenetic Reprogramming in Model Organisms

Worms (*C. elegans*)

Epigenetic reprogramming enables the **appropriate inheritance of histone methylation**. This ensures **germline genes are no longer active** in the developing organism. In *C. elegans*, a microscopic worm, this reprogramming is mediated by two enzymes: **H3K4me2 demethylase SPR-5** and **H3K9 methyltransferase MET-2**.

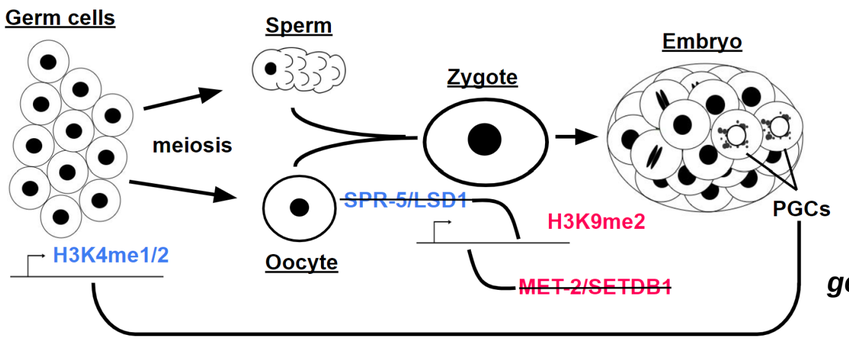

Fig. 2: C. elegans germline reprogramming model.

Mice

In mammals, epigenetic reprogramming is mediated by several enzymes, including **LSD1, an H3K4me1/2 demethylase**, during fertilization.

The hypomorphic LSD1 allele, **M448V**, allows inherited phenotypes to be seen.

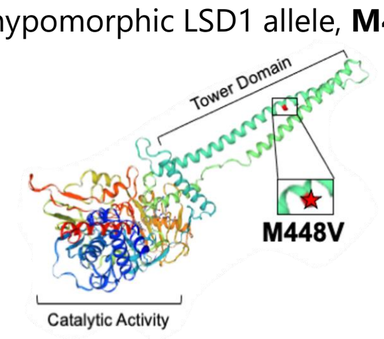

Figure 3: Hypomorphic LSD1. *(Carpenter et. al, Genetics, 2023)*

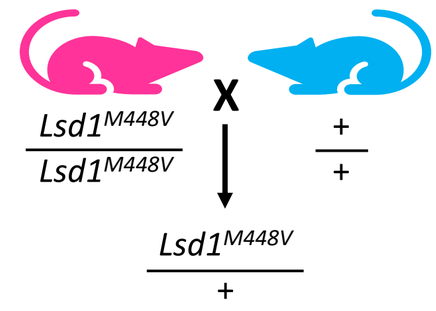

Fig. 4: Maternally Mutant Cross.

Methods & Results

1 Assessing Behavior in Worms

Do C. elegans strains lacking SPR-5 and/or MET-2 enzymes have behavioral defects?

Single-mutant (*spr-5* or *met-2*) **chemotaxis (ability to sense food)** was measured and compared to that of wild type (N2) and double-mutant (*spr-5;met-2*).

The lower the chemotactic index, the greater the behavioral defect.

Double-mutants (DM) possess a severe behavioral defect.

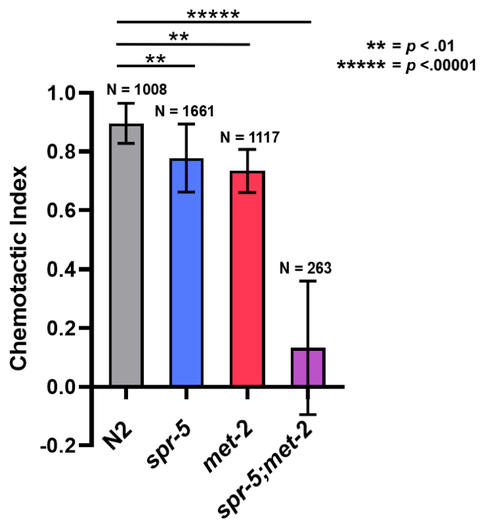

Fig. 4: Chemotactic index of each strain.

2 Rescuing the Behavioral Defect

Is the behavioral defect in the double-mutants caused by a developmental or functional defect in their nervous system?

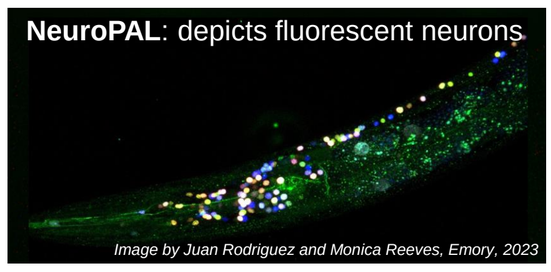

Fig. 5: Intact nervous system in DM.

Lack of a developmental defect in DM nervous system allows behavior to be rescued by turning off germline genes.

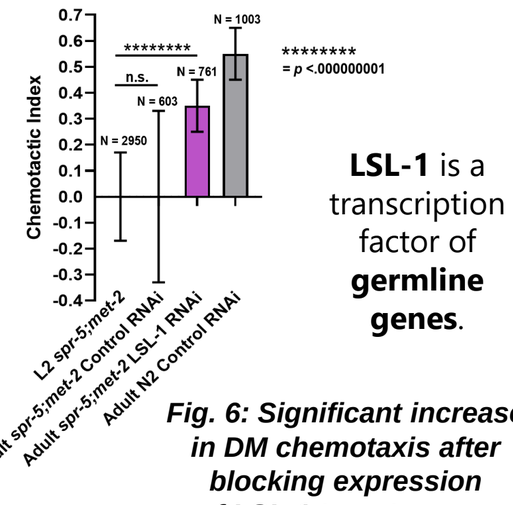

Fig. 6: Significant increase in DM chemotaxis after blocking expression of LSL-1 target genes.

LSL-1 is a transcription factor of **germline genes**.

3 Determining Genes Causing Defect

What are the genes responsible for the behavioral defect in the double-mutant?

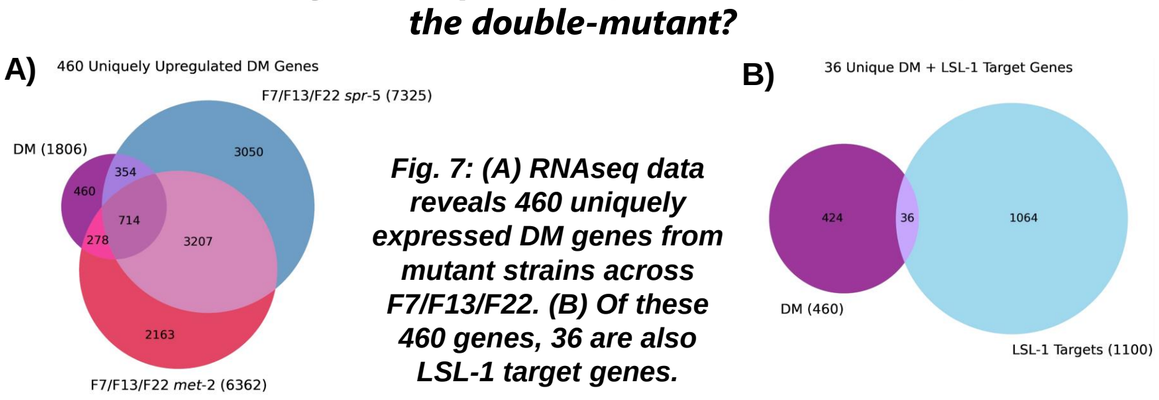

Fig. 7: (A) RNAseq data reveals 460 uniquely expressed DM genes from mutant strains across F7/F13/F22. (B) Of these 460 genes, 36 are also LSL-1 target genes.

The lack of a severe chemotaxis defect in single-mutants suggests that the genes that are both **uniquely expressed in double-mutants** and **LSL-1 targets** must be causing the chemotaxis defect.

There are 36 possible meiotic genes causing the behavioral defect in double-mutants.

4 Assessing Phenotypes in Mice

Do mice with maternally hypomorphic LSD1 suffer from similar phenotypes to those exhibited by human patients?

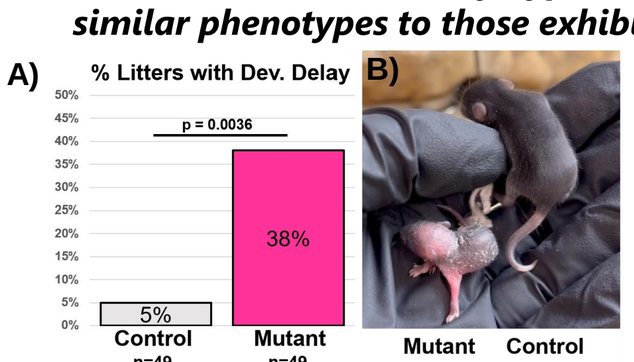

Fig. 8: Developmental delay. (A) *% of litters with 1+ pup with developmental delay is significantly higher in* $Lsd1^{M448V/M448V}$ *than in controls.* ***(B)*** *P10 littermates.*

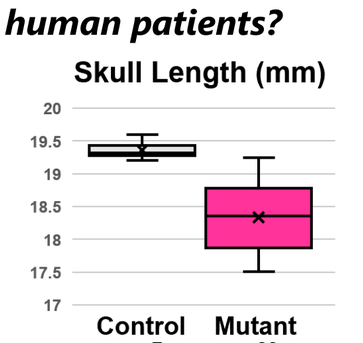

Fig. 9: Craniofacial defects. $Lsd1^{M448V/M448V}$ *progeny skulls are shorter.*

Mice with maternally hypomorphic LSD1 have craniofacial defects and developmental delay.

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