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**
- Mice: Assessing Phenotypes in Mice

**Background: Epigenetic Reprogramming in Model Organisms**

**Worms (C. elegans)**
Epigenetic reprogramming enables the appropriate inheritance of histone methylation. This ensures germine genes are no longer active in the developing organism.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.

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

**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.

2. **Rescuing the Behavioral Defect**
   - Is the behavioral defect in the double-mutants caused by a developmental or functional defect in their nervous system?
   - Lack of a developmental defect in DM nervous system allows behavior to be rescued by turning off germline genes.

3. **Determining Genes Causing Defect**
   - What are the genes responsible for the behavioral defect in the double-mutant?
   - 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.

4. **Assessing Phenotypes in Mice**
   - Do mice with maternally hypomorphic LSD1 suffer from similar phenotypes to those exhibited by human patients?
   - Mice with maternally hypomorphic LSD1 have craniofacial defects and developmental delay.

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.

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- Epigenetic reprogramming is a mechanism that ensures the appropriate inheritance of histone methylation. In C. elegans, a microscopic worm, this reprogramming is mediated by two enzymes: H3K4me2 demethylase SPR-5 and H3K9 methyltransferase MET-2. In mammals, epigenetic reprogramming is mediated by several enzymes, including LSD1, an H3K4me1/2 demethylase, during fertilization.

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