MOLECULAR AND BEHAVIORAL CHARACTERIZATION OF A NOVEL MOUSE MODEL OF SNYDER-ROBINSON SYNDROME: A PATH TOWARDS THERAPEUTIC DEVELOPMENT

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INTRODUCTION

- The polyamines putrescine, spermidine and spermine, are small polycationic molecules essential for normal cell functions such as gene expression, signal transduction and cell proliferation.
- Inborn error of polyamine metabolism due to mutations in *SMS* gene encoding spermine synthase protein causes Snyder-Robinson syndrome (SRS), a rare X-linked recessive disorder which manifests as mental retardation, thin habitus, and low muscle tone (hypotonia) with no available treatment.

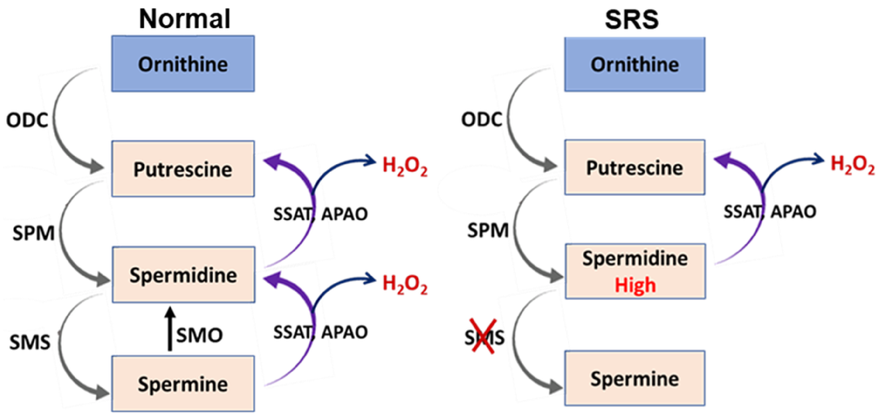

Figure 1. Polyamine metabolic pathway in normal and SRS individual.

- Development of treatment strategy for SRS is hampered by lack of disease specific animal model that recapitulates the phenotypic abnormalities observed in patients.

AIMS

- Characterize the disease pathophysiology in a novel SRS mouse model.
- Develop a genome editing approach to correct the pathogenic mutation and evaluate the therapeutic potential.

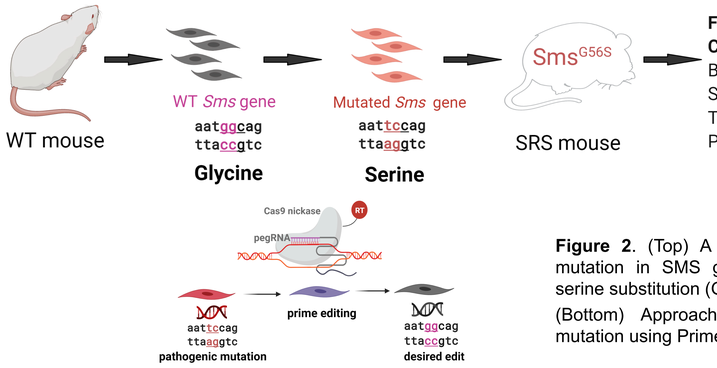

Figure 2. (Top) A novel mouse model carrying mutation in SMS gene leading to a glycine-to-serine substitution (G56S) in the SMS protein.
(Bottom) Approach to correct the pathogenic mutation using Prime Editing.

Missense *Sms* mutation results in complete loss of SMS protein, increases spermidine content and causes muscle degeneration in the G56S mice

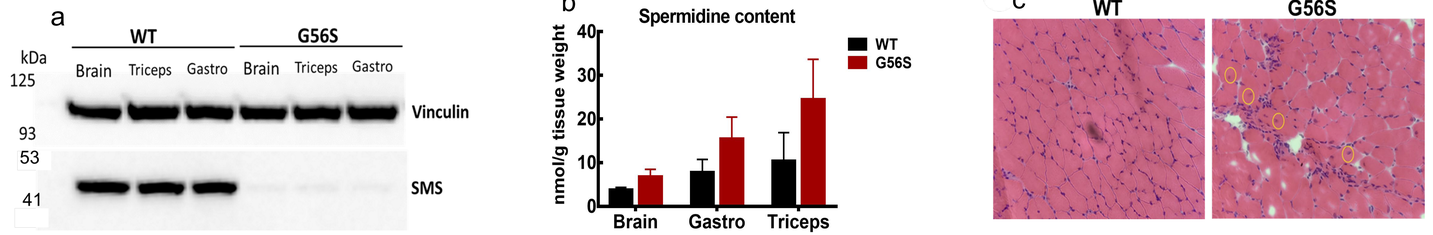

Figure 3 (a) SMS protein determined by western (n=5), (**b**) spermidine content (n=2) in G56S and WT (wildtype) mice tissues quantified by CE-MS, (**c**) Histology analysis of triceps muscle in G56S and WT mice. Scale bar is 180 µm. Circles indicate centralization of nuclei.

G56S mice have significantly reduced body weight, length and bone density compared to the WT

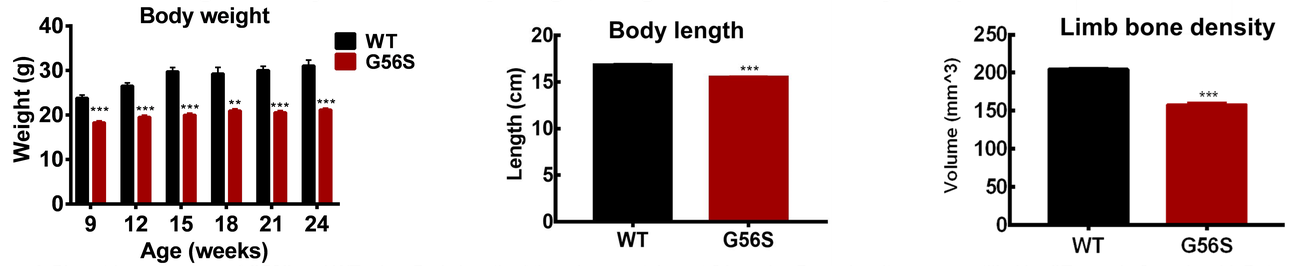

Figure 4. Biometric parameters of G56S and WT mice. Body length of the mice was taken at 24 weeks. Bone density was quantified by CT scan in 6 weeks old. Data shown are mean ± S.E.M, n=7. **p<0.01, ***p<0.001.

G56S mice are less active and exhibited significantly reduce explorative behavior in the center zone of an open field test

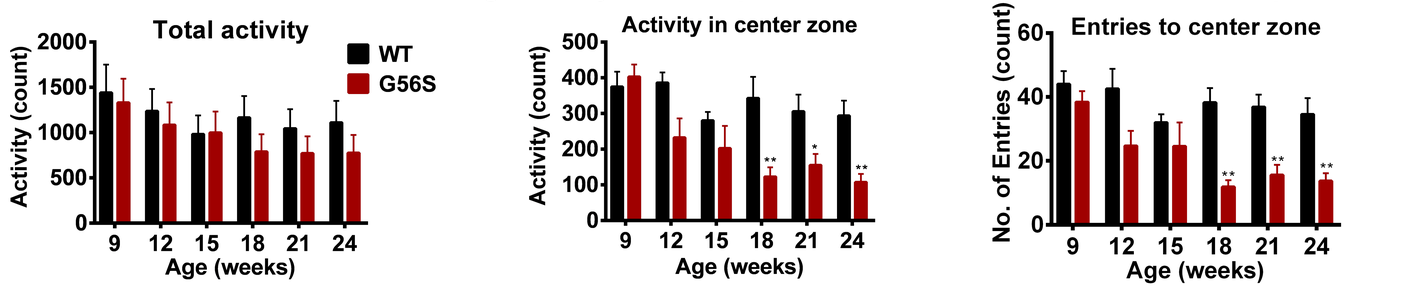

Figure 5. Behavioral activity of G56S and WT mice in open field test. (a) Total activity of both mice in open field, (b) activity of both mice in center region of open field, (c) number of entries to the center region in open field. Data shown are mean ± S.E.M, n=7. *p<0.05, **p<0.001.

CONCLUSION AND FUTURE DIRECTIONS

- The G56S mouse showed molecular and behavioral differences compared to the WT.
- Both analyses suggest that the G56S mouse mimics the abnormalities seen in SRS patients.
- We are currently testing prime-editing to correct the pathogenic mutation in the *SMS* gene and to rescue the phenotypic abnormalities in the G56S mouse.

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