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Functional characterization of two genes deleted in Phelan McDermid Syndrome: SHANK3 and SULT4A1

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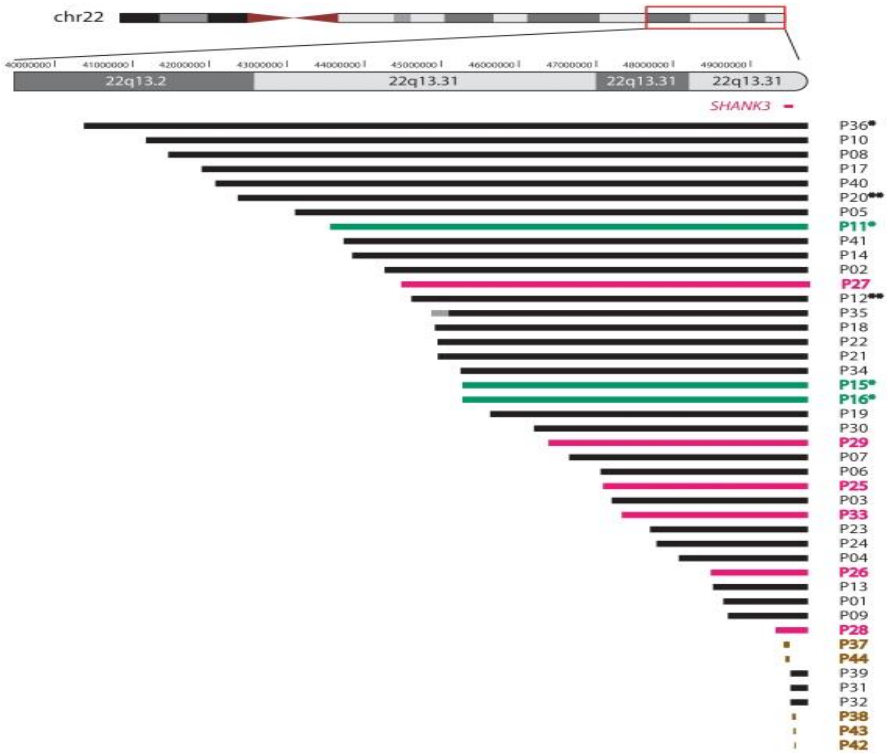
EPTRI Open Meeting 03-04-2020

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 777554

PHELAN-McDERMID SYNDROME (PMS)

Summary

- ✓ Global developmental delay
- ✓Absent or delayed language
- ✓ASD like behavior
- ✓Neonatal hypotonia
- ✓Normal to advance growth
- ✓Epilepsy



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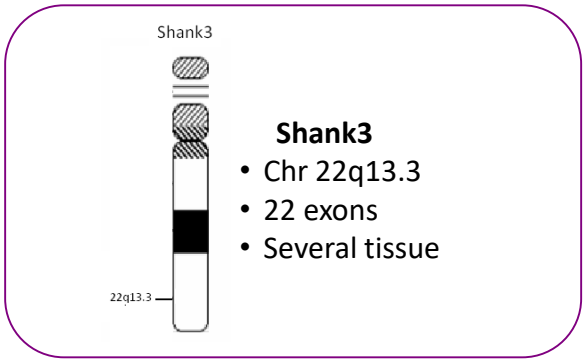
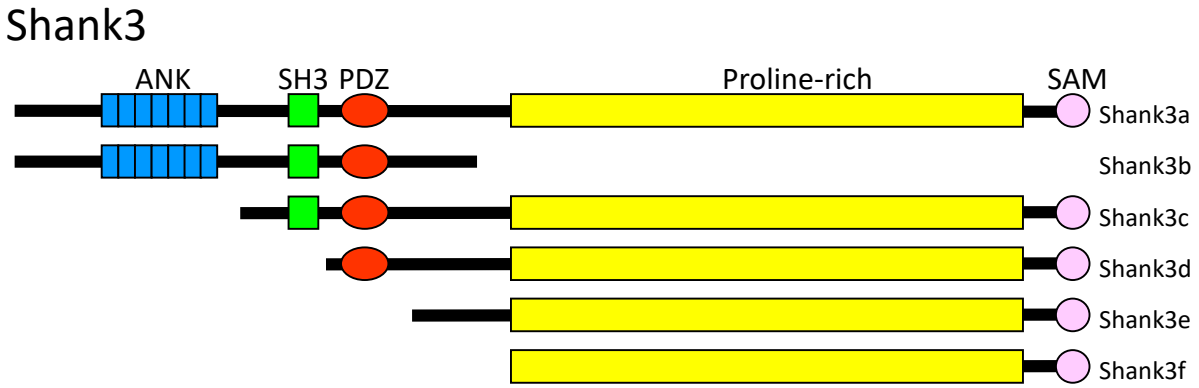
Shank3 and PMS

Shank3





Model to study Shank3 functions

- Repetitive, stereotyped behavior
- Reduced Sociability
- Impairments in spatial learning and memory

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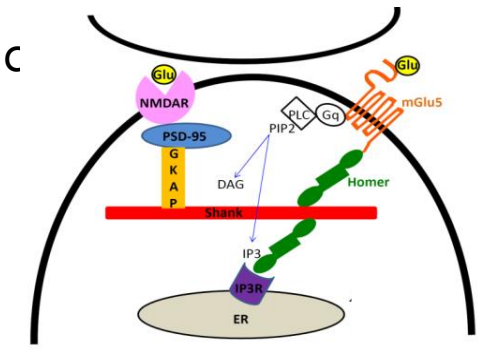
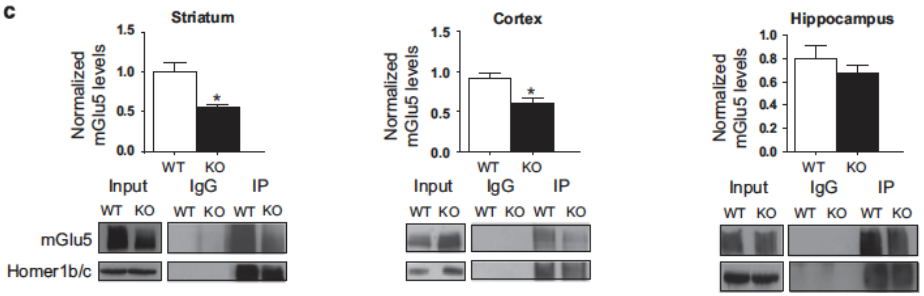
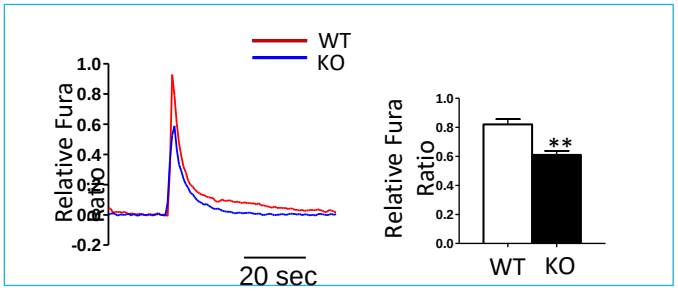


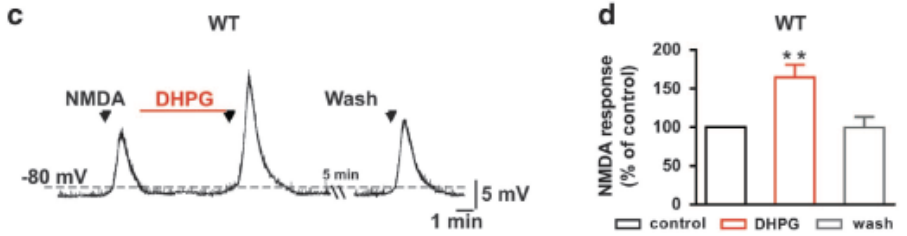
Homer and mGlu5 interaction is reduced in striatum and



Shank3 deletion impairs mGlu5-mediated intracellular calcium release in cortical neurons



Shank3 deletion affects mGlu5 signalling in striatal neurons



Both defects are rescued by mGlur5 Positive Allosteric Modulators

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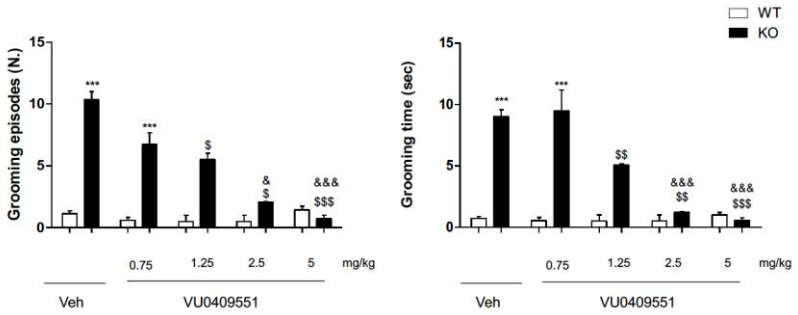
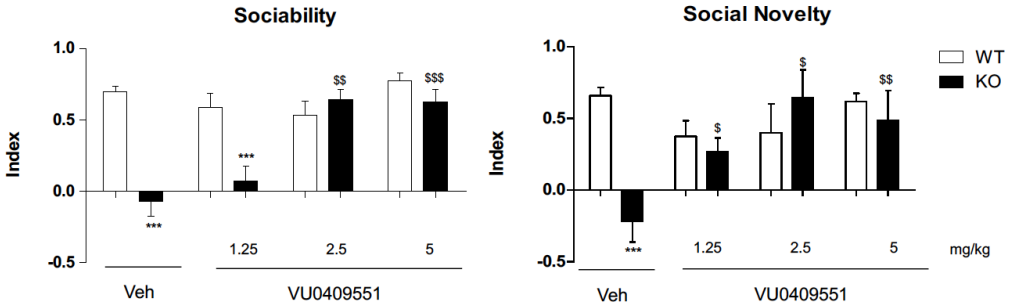
Shank3 and PMS

VU0409551 ameliorates ASD-like behavior of Shank3 (11) KO mice

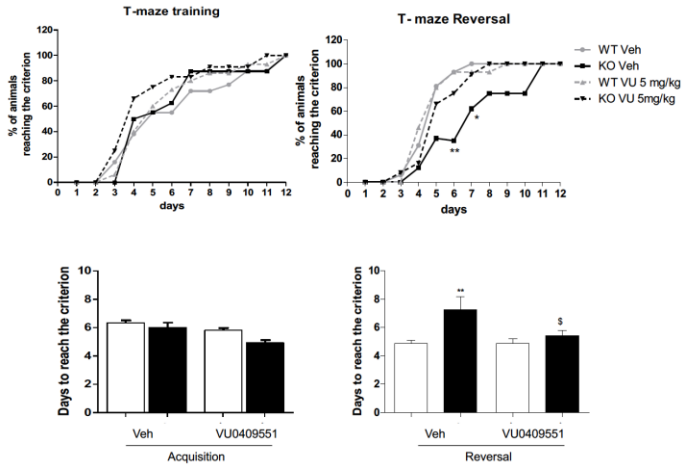
- Repetitive, stereotyped behavior



- Sociability



- Cognitive rigidity



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Shank3 and PMS

Summary I

1. Shank3 deletion impairs mGlu5 and Homer synaptic localization specifically within the cortex and striatum

2. This impairment leads to an alteration of mGlu5 intracellular signaling

3. ASD-like behavioral defects, such us repetitive behavior, impaired sociability and reduce memory flexibility, observed in Shank3 11 mice can be ameliorated by increasing mGlu5 activity through PAMs treatment

4. Therefore mGlu5 is an excellent candidate for the study of new pharmacological treatments of ASD-like symptoms and mGlu5 PAMs may represent a new approach for treating patients affected by PMS and/or Shank3 deletions.

SULT4A1 and PMS

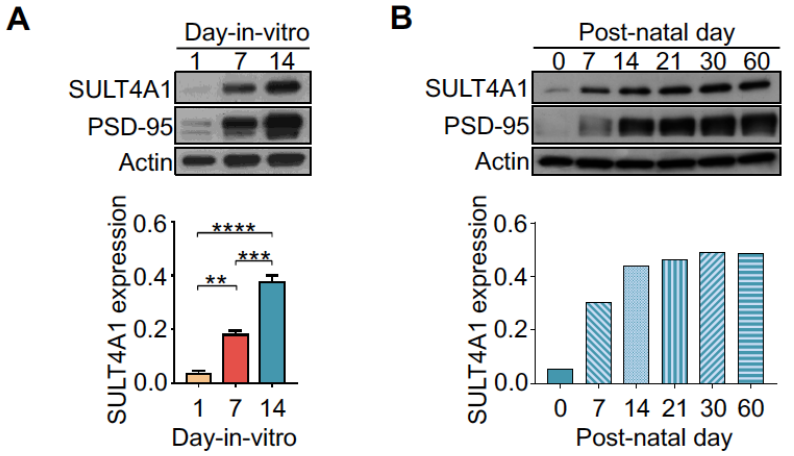
Approximately 30% of patients with PMS have a deletion encompassing SULT4A1

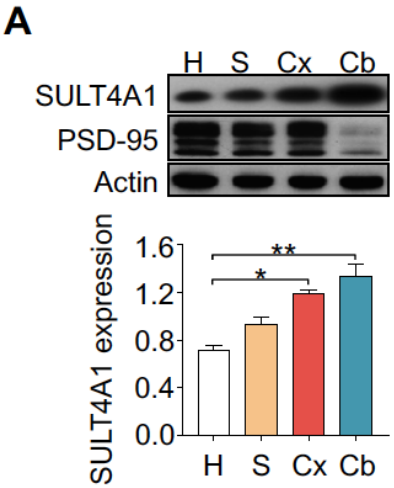
SULT4A1

SULT4A1 is selectively expressed in neurons

SULT4A1 polymorphisms also may be linked to schizophrenia risk

Decrease in SULT4A1 mRNA levels in bipolar patient (dorsolateral prefrontal cortex)





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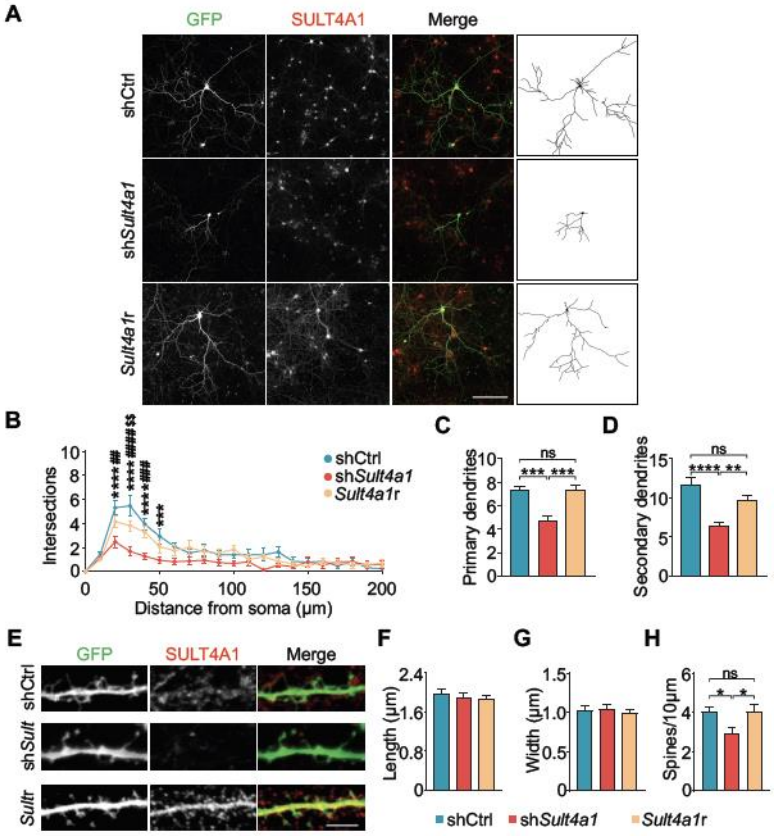
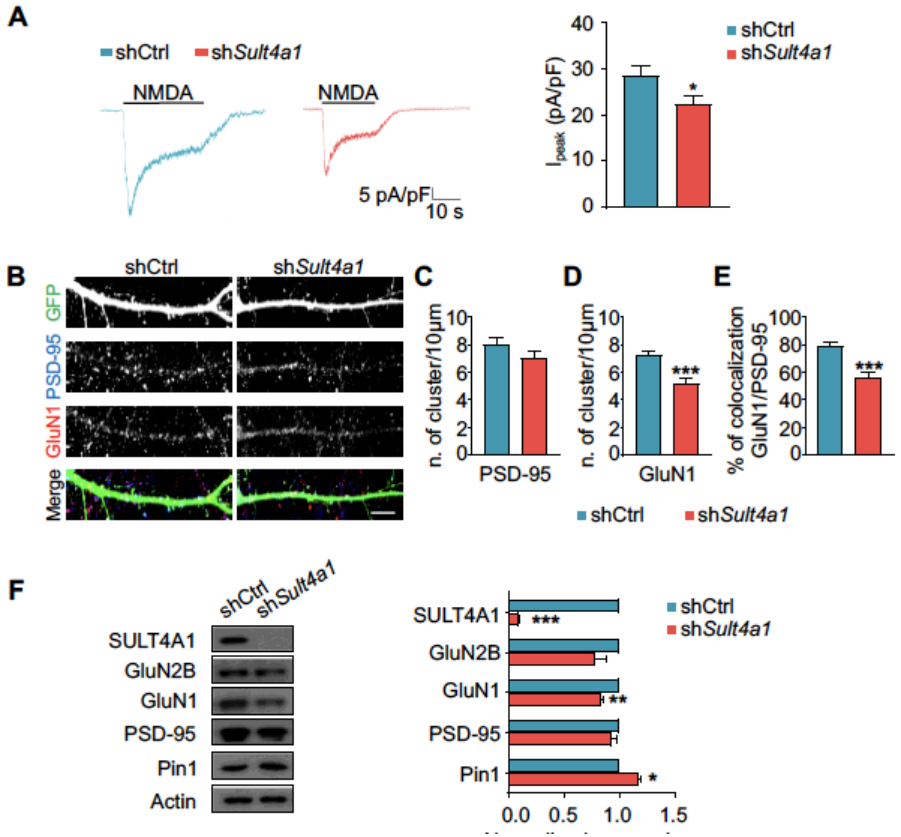
SULT4A1 and PMS

SULT4A1 silencing reduces neuronal arborization and spine density



SULT4A1 modulates NMDAR activity



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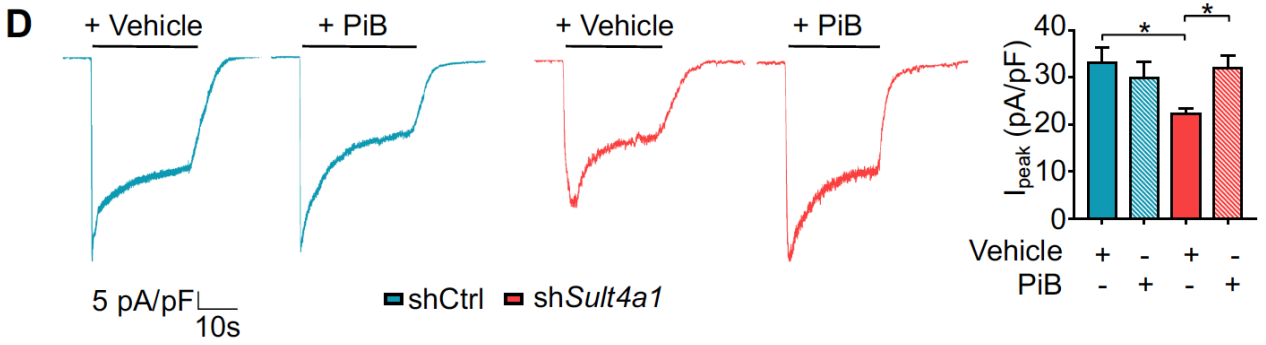
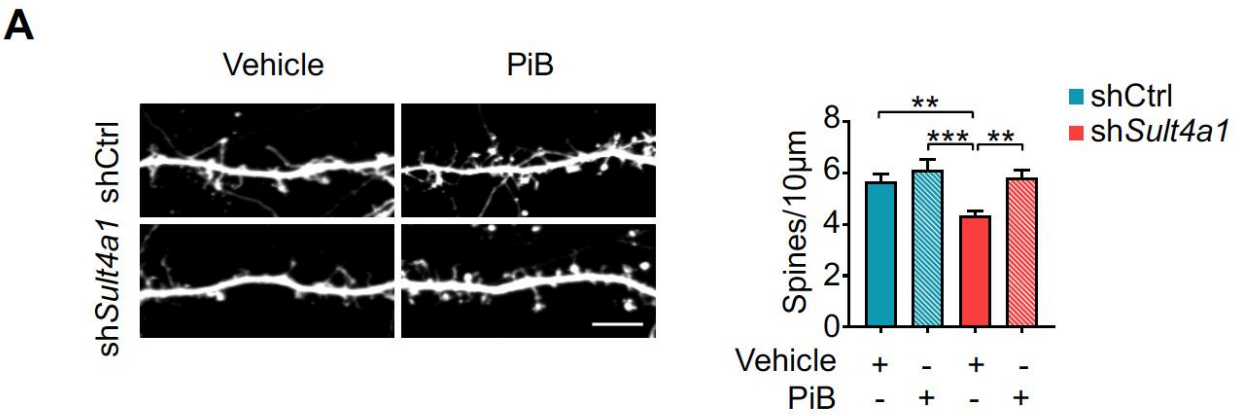
SULT4A1 and PMS

Pin1 inhibition rescues NMDA currents in SULT4A1-knocked down neurons



Pin1 inhibition restores the number of dendritic spines in SULT4A1-knocked down neurons



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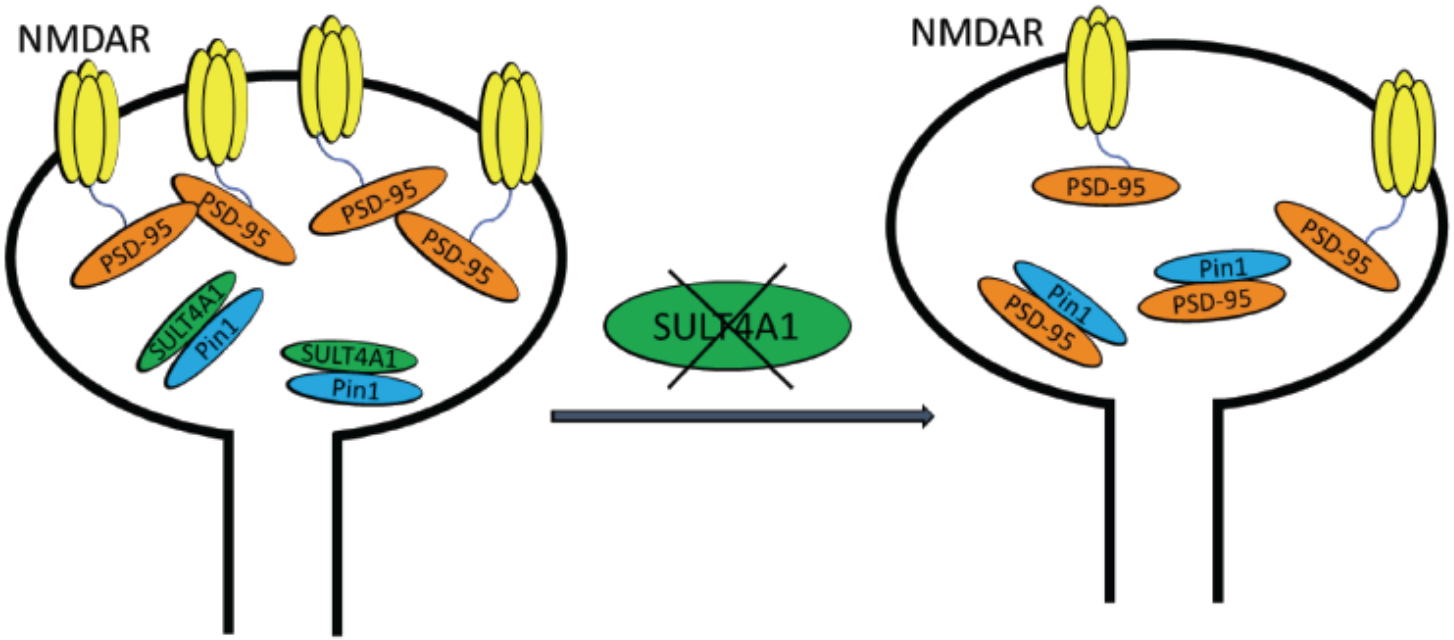
SULT4A1 and PMS

SULT4A1 modulates NMDAR synaptic expression and function.



Our data suggest that SULT4A1 might be related with the neurological sympoms found in PMS patients

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 777554