Autism associated Shank3 mutations alter skeletal muscle maturation: therapeutic strategies using 3D-bioprinted skeletal muscles

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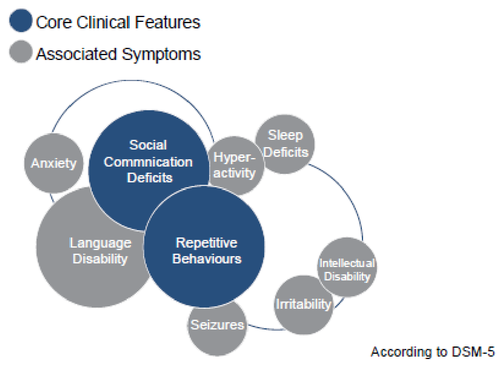
INTRODUCTION

Autism spectrum disorders



According to DSM-5

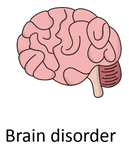
Autism spectrum disorders are:

- Heterogenous group of neurodevelopmental disorders
- affecting 1-2% of the population
- caused by the novo mutations in 10.20% of the cases

Shank3 in ASD

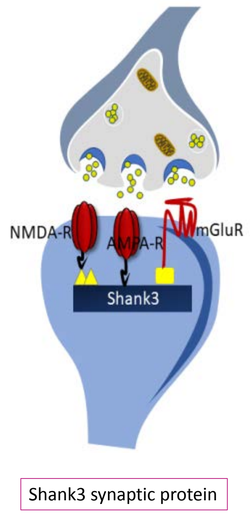
Phelan-McDermid Syndrome

- Frequency 0.69%
- Chr 22p13.3 (mutations in Shank3 gene))
- **neonatal hyptonia**
- Autism
- intelectual disability
- Global developmental delay
- absent delayed speech

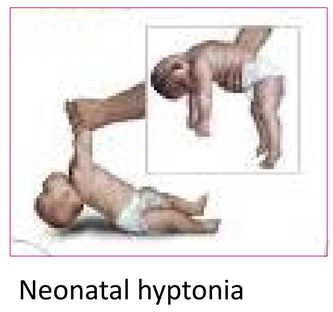


Brain disorder

Synapse



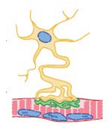
Shank3 synaptic protein



Neonatal hyptonia

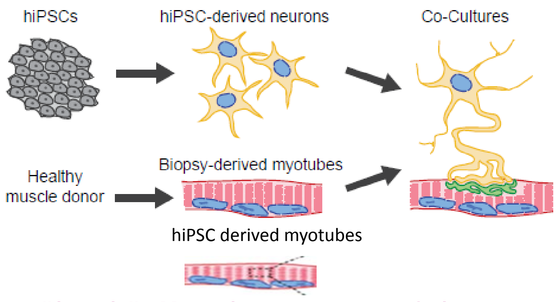
Aim of the study

Effects of Shank3 deficency in at the neuromuscular juntion and striated muscle



Methods and Results

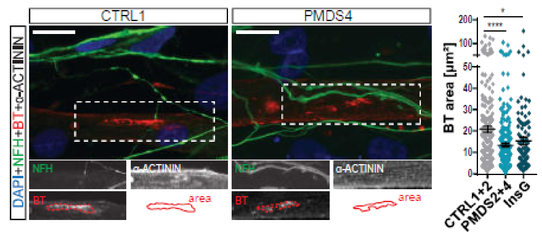
Generation of induced pluripotent stem cells lines

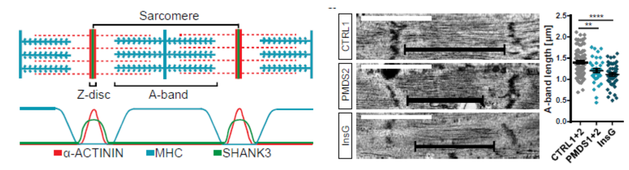


Healthy donor
PMDS patients (Shank3 mutation)
Point mutation (InG) inserted via Crispr/CAS9

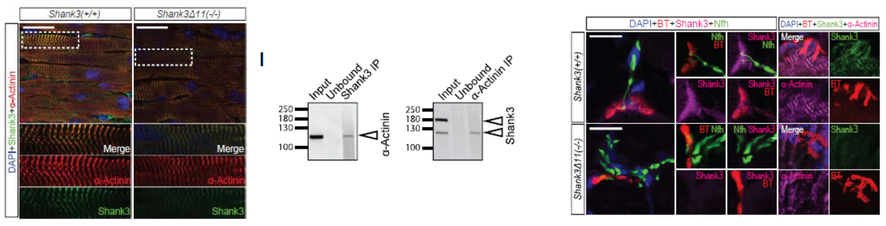
Shank3 Knock mouse model

Shank3 deficiency induces impairment of the clustering Acetycholine receptors and thinning of the sarcomere A-Band

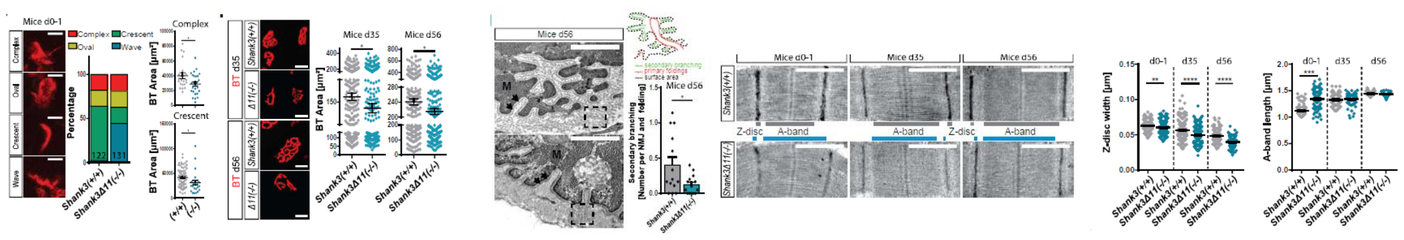




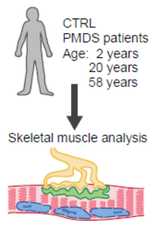
Shank3 forms a complex with actinin at the sarcomere and also localises at the neuromuscular juntion



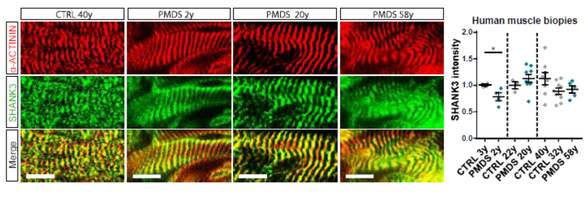
Neuromuscular Junction foldings and sarcomere z-disk are altered Shank3 knock mice



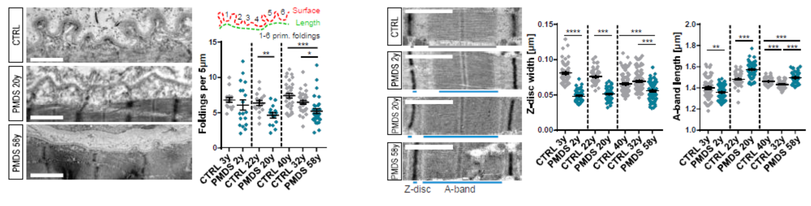
Muscle biospsies from patients carrying a Shank3 mutation



In human muscles Shank3 colocalises with actinin at the sarcomere Shank3 levels are altered in patients



Neuromuscular Junction foldings and sarcomere z-disk are altered in Shank3 patients

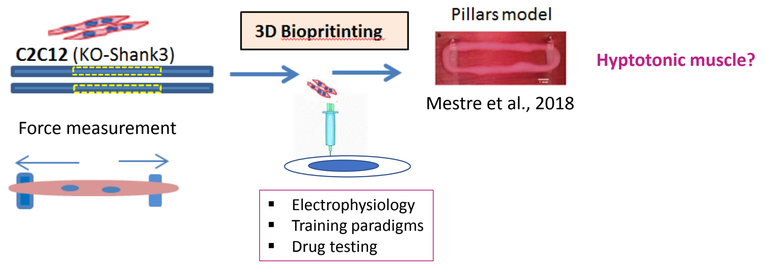


CONCLUSIONS

- Shank3 localises at the neuromuscular juntion and Z-discs of striated muccles
- Shank3 is a fundamental protein in the maturation of these motor unit components
- Shank3 deficiency may be directly associated with neonatal hyptonia
- Opens a therapeutic window

Future work

Modelling and treating Shank3 associated hypotonia in a dish



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