MYT1L haploinsufficiency in human neurons and mice causes reversible autism-associated phenotypes

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GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION

Research for a Life without Cancer

"The brain's utter centrality in the cockpit of our being means its malfunctions are unusually dangerous and far-reaching, attacking not just our health but our whole sense of self in particularly damaging and debilitating ways"

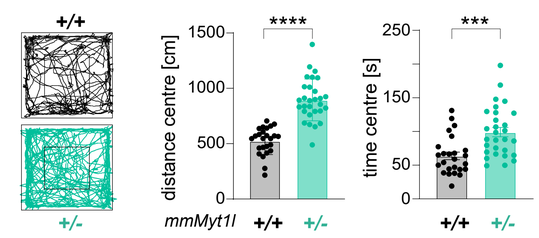
The transcription repressor MYT1L

- neuron specific [1]
- life-long expressed [1]
- important for neuronal cell identity [2]
- mutations are strongly linked to mental disorders such as autism spectrum disorder (ASD), schizophrenia and intelectual disability [3,4]

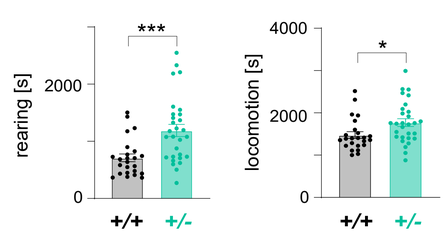
Can Myt1l mutations be causative for neuropsychiatric disorders?

Behavioural abnormalities in *Myt1l*-mutant mice

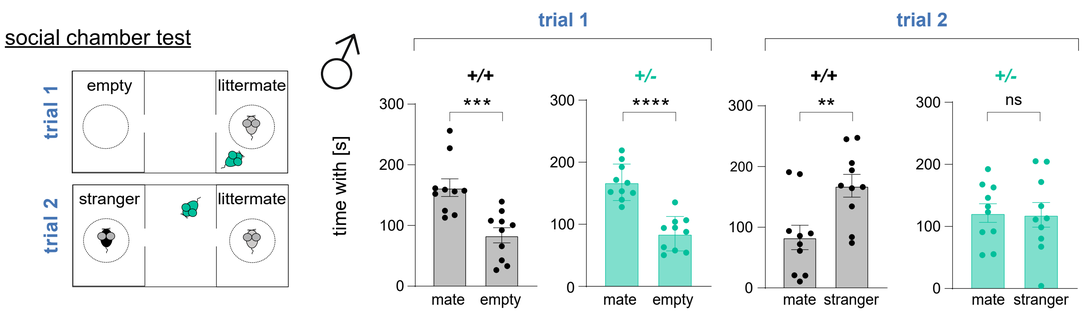
Open field



Home cage

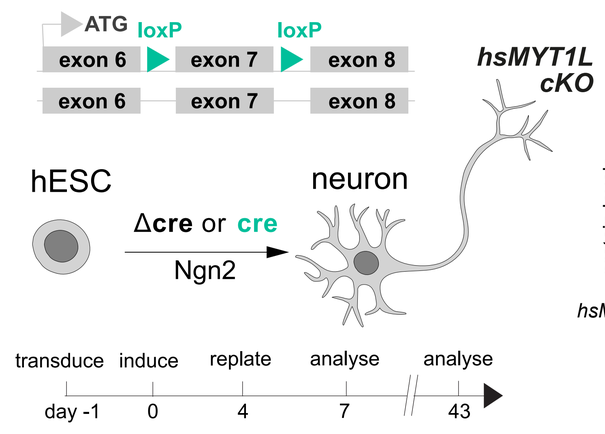


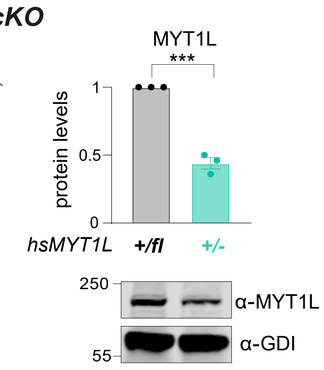
social chamber test

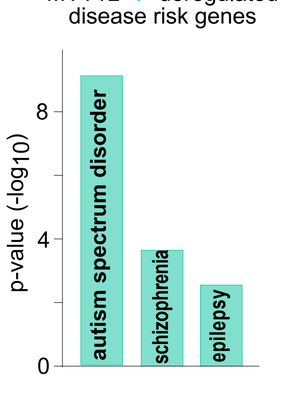


Heterozygous Myt1l-knockout mice are hyperactive and males present with social deficits

Disease modelling with human induced neurons

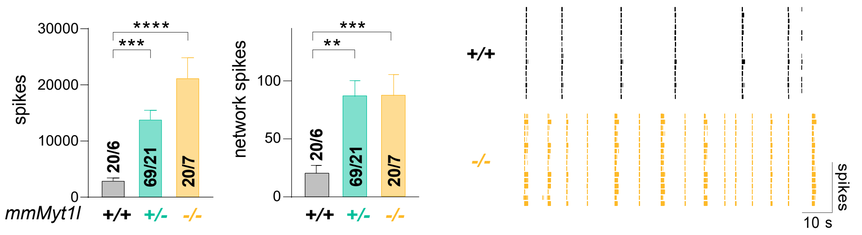






Human embryonic stem (hES) cells can be engineered to carry inducible loss-of-function mutations and can be differentiated into induced neurons (iN) by overexpression of the proneural transcription factor Ngn2 [5].

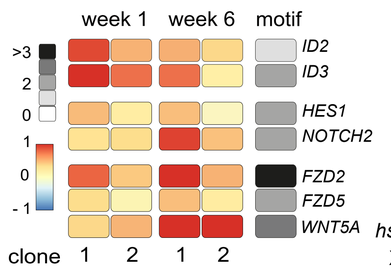
Conserved electrophysiological phenotypes in both models

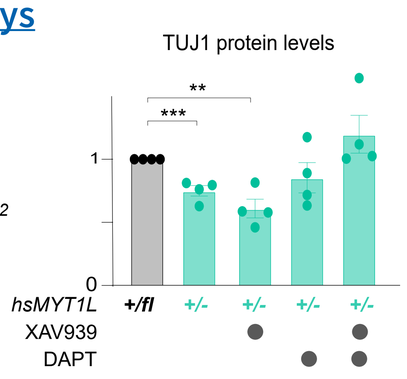


As in human induced neurons, Myt1l-depleted primary hippocampal cultures show increased network activity

Impaired repression of developmental pathways

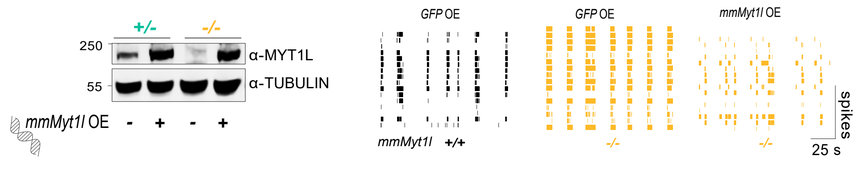
Increased expression of negative regulators of neurogenesis upon MYT1L depletion results in impaired differentiation of induced neurons, which can be rescued by chemical inhibition of WNT/NOTCH signalling





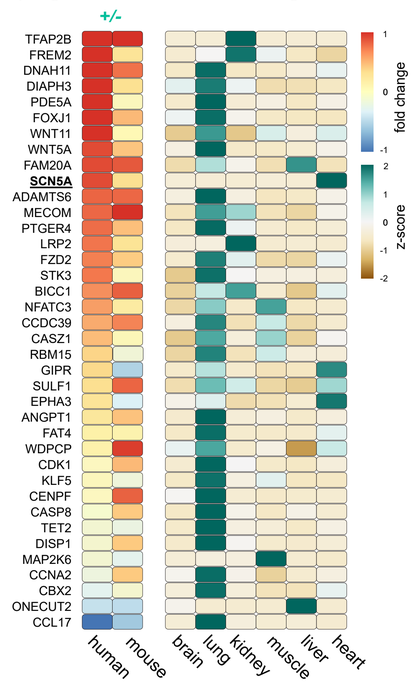
Genetic and pharmacological rescue

MYT1L overexpression

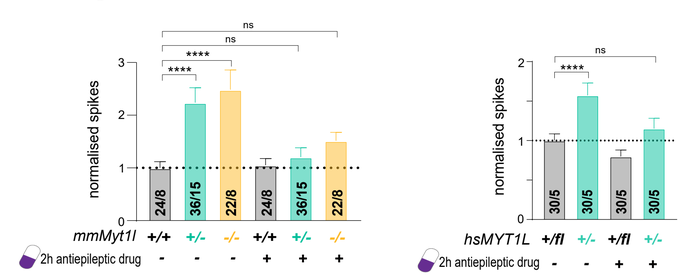


MYT1L overexpression in postmitotic primary mouse neurons reduces spiking frequency

Upregulation of non-neuronal genes

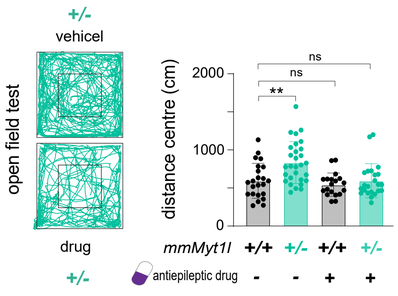


Acute drug treatment *in vitro*



Pharmacological rescue in mouse and human cultures

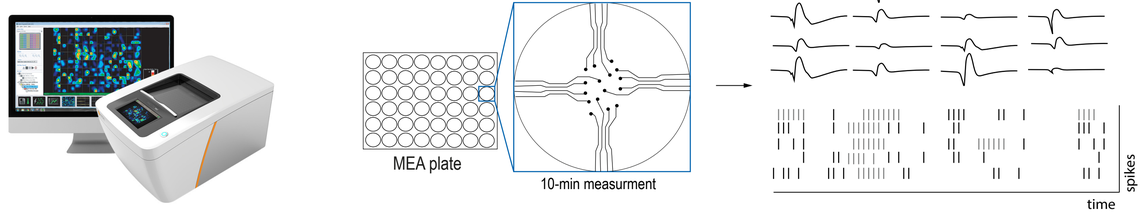
Drug injection into mice



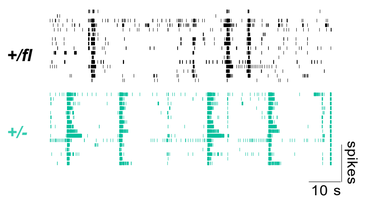
Behavioural abnormalities can be normalised by drug treatment

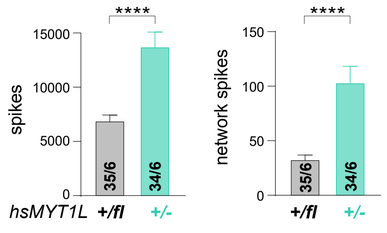
High-throughput measurement of field potentials

Multi-electrode array (MEA)



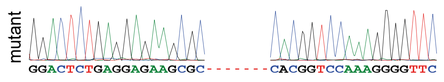
Impaired electrophysiological activity



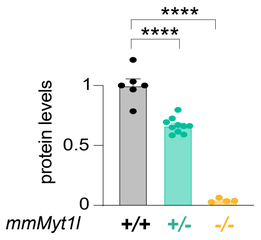


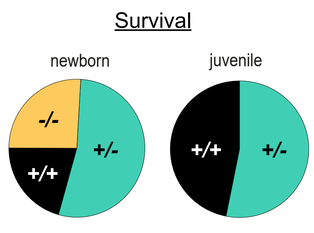
Increased network activity of MYT1L-depleted human induced neurons

Emphasising the importance of MYT1L in a knockout mouse model

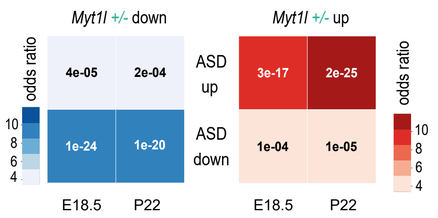


7-bp deletion *mmMyt1l* exon 6





similar gene deregulation as in ASD patients



Myt1l expression is essential for survival and gene deregulation in heterozygous Myt1l-knockout mice resembles ASD patients

Key points

MYT1L mutations in human and mouse models result in gene deregulation that resembles ASD patients

Myt1l-mutant mice are hyperactive and present with male-specific social deficits

MYT1L-deficient primary mouse and human induced neurons show increased electrophysiological activity, which can be normalised by MYT1L overexpression in postmitotic primary mouse neurons

Application of an FDA-approved antiepileptic drug rescues electrophysiological and behavioural phenotypes

Bar graphs display mean values with number of MEA wells and cells from indicated biological replicates or data points from individual animals and iN batches, error bars = SEM, * p < 0.05, ** p < 0.01, *** p < 0.001, **** p < 0.0001, ns = not significant.

[1] Cardoso-Moreira et al., Gene expression across mammalian organ development, Nature 2019
[2] Mall et al., Myt1l safeguards neuronal identity by actively repressing many non-neuronal fates. Nature 2017
[3] Coursimault et al., MYT1L-associated neurodevelopmental disorder: description of 40 new cases and literature review of clinical and molecular aspects, Human Genetics 2021
[4] Simons Foundation Autism Research Initiative
[5] Zhang et al., Rapid single-step induction of functional neurons from human pluripotent stem cells. Neuron 2013

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