Poster 226

Neonatal AAV Gene Therapy Rescues Phenotypes in STXBP1 Haploinsufficient Mice

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Overview

QUESTION

Does pre-symptomatic treatment with a GT rescue relevant disease symptoms in a mouse model of STXBP1 haploinsufficiency?

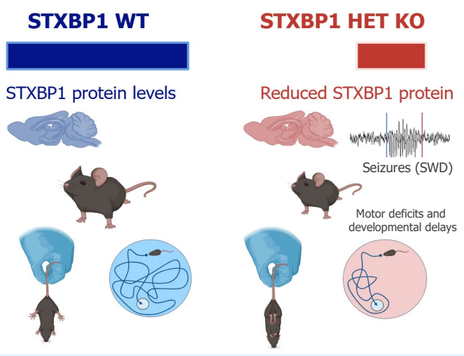
INVESTIGATION

We explored the administration (ICV) of a novel AAV GT in STXBP1 transgenic mice and measured the impact on disease symptoms up to 6 months

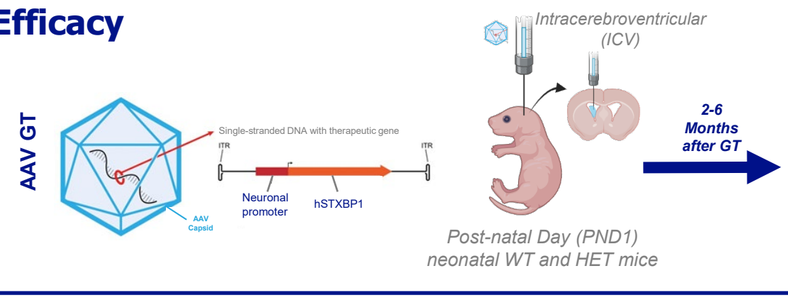
RESULTS

Preclinical Model

STXBP1 HET KO mice have reduced STXBP1 protein levels and present a robust disease phenotype with reduced body weight, frequent absence seizures, motor and cognitive deficits



Efficacy



- ✓ Increase of total STXBP1 protein levels across wide brain areas
- ✓ Reduced seizure frequency with potential for seizure freedom
- ✓ Improvement of motor and cognitive symptoms
- ✓ Recovery of body weight

CONCLUSIONS

AAV GT administered at PND1 via ICV in STXBP1 haploinsufficient mice enables widespread STXBP1 expression and rescues disease phenotypes, supporting its potential as a disease modifying therapy

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Background

STXBP1 disorders are linked to a loss of function of the syntaxin-binding-protein-1 (STXBP1) and are associated with severe neuronal development delay, intellectual disability and seizures. There are currently not efficacious treatments for this developmental disease.

Objective

In this study, we evaluated the potential of a gene therapy (GT) approach administered at neonatal age to modulate disease symptoms in a STXBP1 heterozygous knock-out mouse model

Methods

STXBP1 heterozygous (HET) KO mice have been licensed from the University of Amsterdam. AAV constructs encode the WT human STXBP1 and HA tag under the control of a neuronal promoter. Animals have been injected at post-natal day 1 (PND1) using intra cerebroventricular administration (ICV) with either vehicle or AAV treatment. EEG recordings were performed in group housing video-EEG wireless telemetry platform (24 hours/day). A battery of behavioral tests was performed to evaluate motor and cognitive performances. Biochemical analysis of transgene expression was performed in prefrontal cortex tissue using qPCR, Western Blot and LC-MS. Immunohistochemistry analysis using HA-tag antibodies was performed on fixed sagittal brain slices.

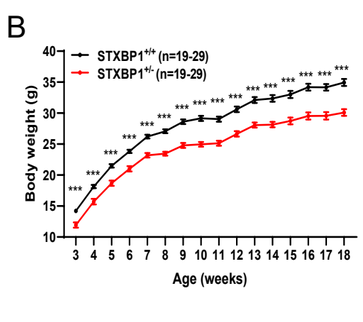
Results

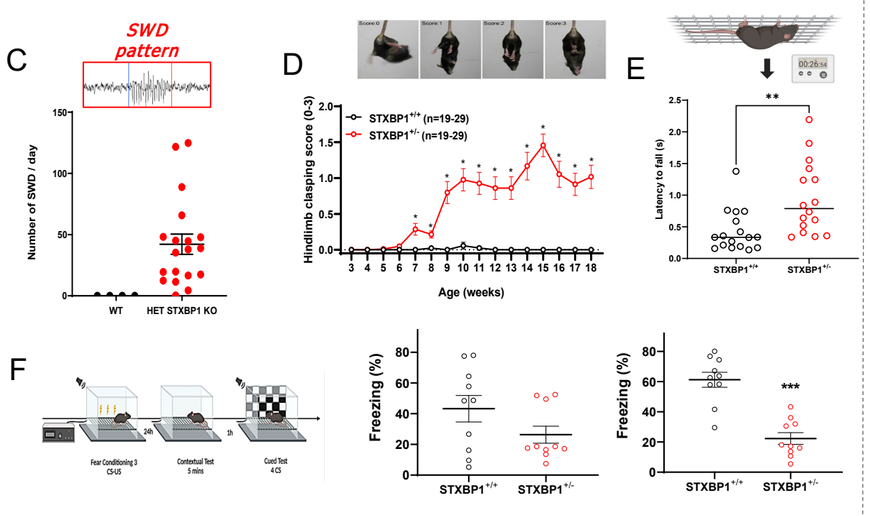
STXBP1 preclinical mouse model

The disease symptoms of STXBP1 HET mice have been extensively characterized and have been reported previously[4] (*see Table 1*)

A

Symptoms	Test	Phenotype
Growth deficit	*body weight*	↓
Epilepsy	*EEG (SWD)*	↑
Motor dysfunction	*Hindlimb clasping (dystonia)*	↑
	Wire hanging (muscle strength)	↑
Cognitive deficit	*Fear conditioning (associative learning memory)*	↓
Psychiatric disorders	*Open field (hyperactivity)*	↑
	Open field (Moonwalking)	↑



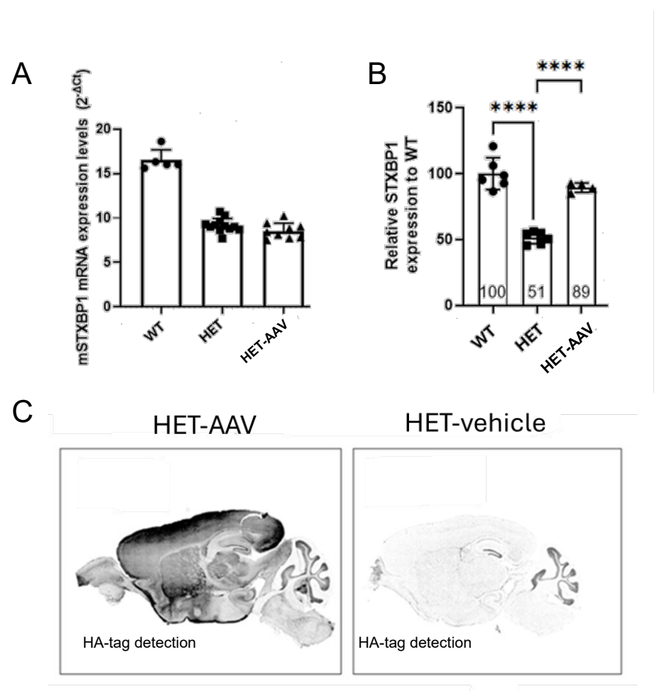


Phenotypic characterization of STXBP1 HET (STXBP1+/−) mice.
(A) Summary table of observed symptoms, corresponding electrophysiological and behavioral tests, and direction of phenotypic changes in STXBP1+/− mice compared to wild-type (WT).
(B) Longitudinal body weight measurements showing reduced growth in STXBP1+/− mice from early postnatal stages through adulthood.
(C) Quantification of spontaneous spike-and-wave discharges (SWDs) per day, indicating increased absence seizure activity in STXBP1+/− mice.
(D) Hindlimb clasping scores across age, demonstrating progressive motor dysfunction in STXBP1+/− mice.
(E) Wire hanging test, demonstrating progressive motor dysfunction in STXBP1+/− mice.
(F) Fear conditioning test, demonstrating progressive cognitive dysfunction in STXBP1+/− mice.

Efficacy of neonatal presymptomatic AAV GT in STXBP1 transgenic mice

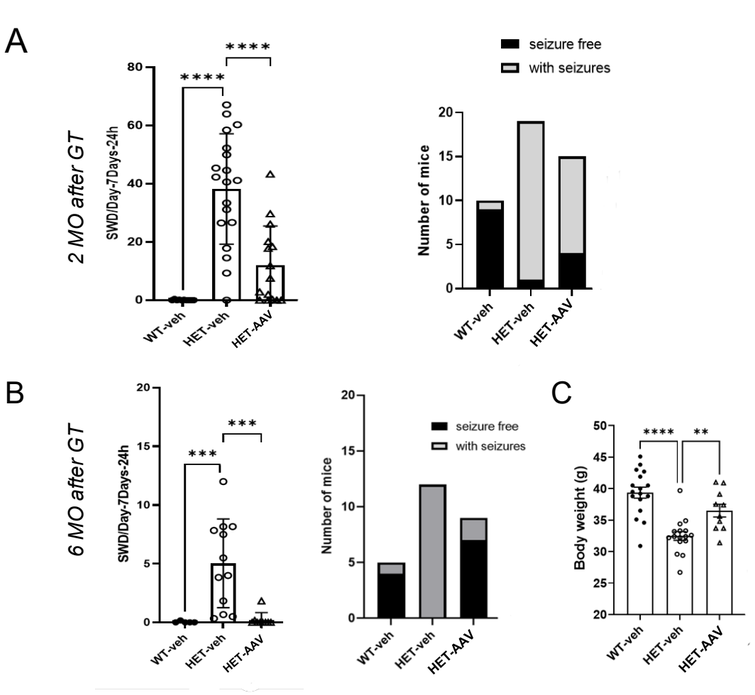
AAV GT administered ICV increases total STXBP1 levels and provides a brain-wide distribution

AAV GT led to a significant increase and rescue of the total STXBP1 protein levels in the mouse brain. Biochemical analysis was performed in the prefrontal cortex 6 months after GT. (A) qPCR analysis indicates that GT does not affect endogenous mouse STXBP1 levels. (B) Western Blot analysis shows a ~50% reduction in STXBP1 brain levels in the HET mice and which could be rescued by the GT. (C) Distribution of HA-STXBP1 in mouse brain by IHC.



GT reduces spike-wave discharges (SWD) and normalized bodyweight

STXBP1 HET mice have a lower body weight and develop frequent spike wave discharges. SWD were recorded by EEG 24/7 and the frequency was recorded in WT, HET and AAV treated animals at 2 months (A) and 6 months (B) of age. GT led to a robust and significant reduction in the SWD frequency after 2 months and to an almost complete suppression after 6 months and which is also reflected by the number of "seizure free" mice. The animal body weight was followed weekly over a 6 months period (C) and GT was able to partially rescue the reduced body weight in HET mice.

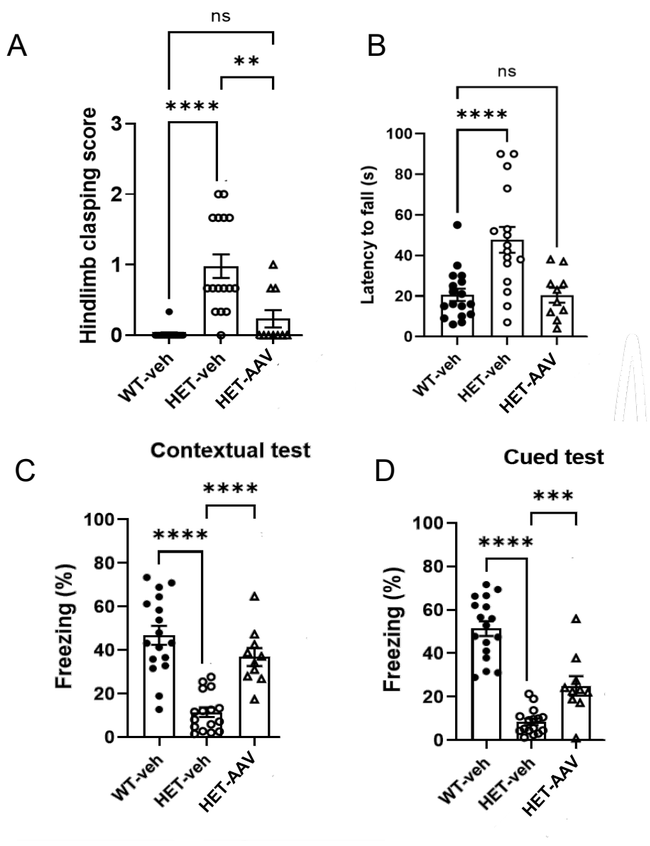


All data in this poster are shown as mean values with individual data points to illustrate variability within each group.

Improved motor and cognitive performance of STXBP1 HET mice after GT

This figure illustrates the outcomes of behavioral testing. (A) Hindlimb clasping scores were elevated in HET mice, indicating motor abnormalities. Treatment with AAV reduced these scores, suggesting partial improvement in motor function. (B) In the wire hanging test, which measures balance and coordination, HET mice showed increase ability to stay holding the grid. AAV treatment restored performance showing a sign toward motor improvement.

(C) In the contextual fear conditioning test, WT mice displayed strong memory of the environment associated with a mild shock, while HET mice showed reduced memory. AAV-treated mice exhibited intermediate performance, indicating partial rescue of contextual memory.(D) In the cued fear conditioning test, which assesses memory of a sound cue, WT mice again showed strong recall, while HET mice had impaired responses. AAV treatment improved performance, though not to WT levels.



Conclusions

This study demonstrates that intracerebroventricular (ICV) administration of AAV gene therapy (overexpressing hSTXBP1) at postnatal day 1 (PND1) in STXBP1 haploinsufficient mice enables widespread overexpression of STXBP1 across the brain. This early intervention leads to measurable improvements during adulthood in disease-relevant phenotypes, including motor coordination and cognitive performance. These findings highlight the therapeutic potential of neonatal AAV-based gene therapy for STXBP1-related neurodevelopmental disorders.

References

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4. Rodriguez et al., AES Orlando 2023, Poster 1.112

UCB-sponsored. UCB was involved in the design of the study, the collection, analysis, and interpretation of data, and review of the poster.

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36th International Epilepsy Congress
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