Dopamine transporter dysfunction in the high-risk schizophrenia 3q29 deletion mouse model

Sindhu Sriramoji-Virdi, Rebecca Pollak, Jennifer Mulle and Miriam Bocarsly
Rutgers New Jersey Medical School, Department of Pharmacology, Physiology and Neuroscience and Rutgers Brain Health Institute

RUTGERS New Jersey Medical School

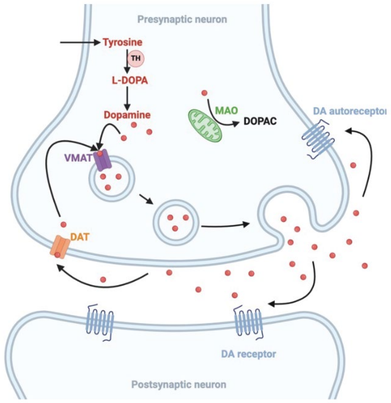
Introduction & Background

- The 3q29 microdeletion presents a >40-fold higher risk for developing schizophrenia, a debilitating disorder that affects behavior, cognition, and emotional regulation in humans.
- Striatal dopamine dysregulation has been suggested to play a role in schizophrenia symptomology and remains unexplored in 3q29 deletion patients.
- This study utilizes a CRISPR CAS9 mouse model (3q29del) of the human genetic disease. (Rutkowski et al. 2019)
- 3q29del mice show reduced brain volume and exhibit several behavioral impairments, including deficits in social interaction, altered acoustic startle responses, and heightened sensitivity to amphetamines. (Rutkowski et al. 2019)

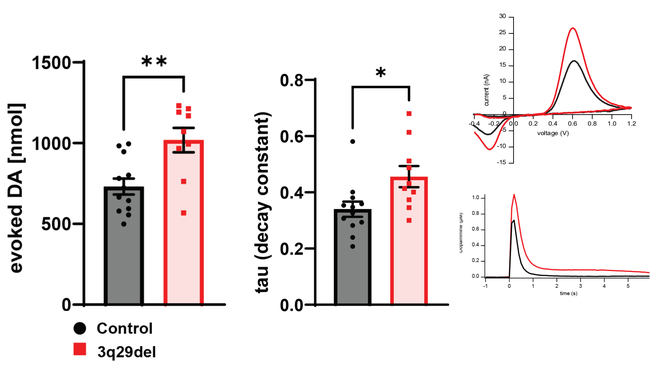
Methods

- Ex vivo fast-scan cyclic voltammetry was performed in the dorsal striatum of 3q29del and littermate control mice to assess dopamine signaling.
- Dopamine transporter (DAT) function and expression were analyzed using qPCR, protein quantification and ligand binding.

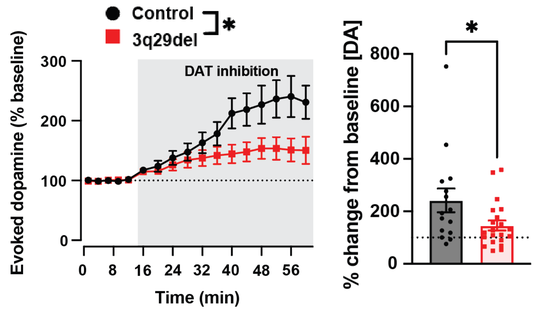
Results



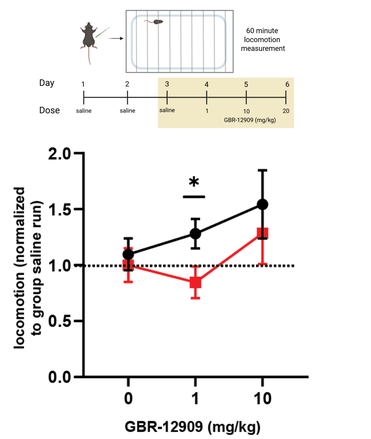
1 3q29del mice have elevated dopamine in the dorsal striatum and impaired dopamine clearance.



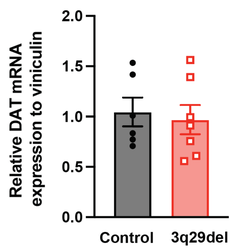
2 3q29del mice have lowered DAT activity in the dorsal striatum.



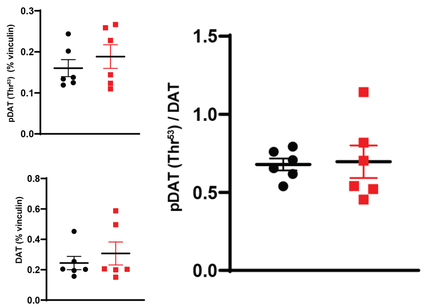
3 3q29del mice have an attenuated response to selective DAT inhibitor.



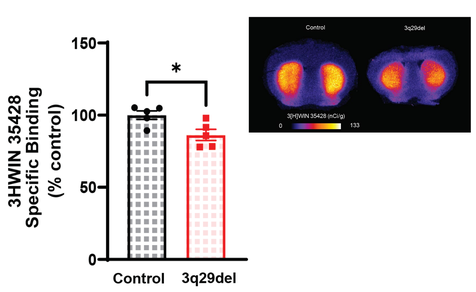
4 DAT mRNA expression is unchanged in 3q29del mice.



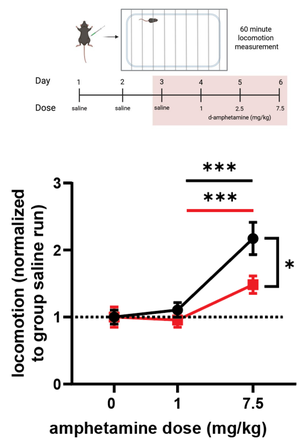
5 DAT and p-DAT protein expression is unchanged in 3q29del mice.



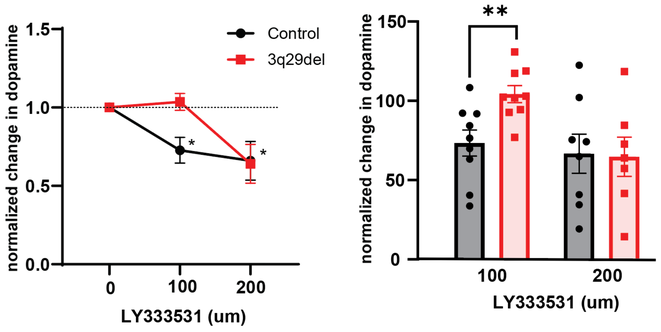
6 3q29del mice show less DAT binding availability.



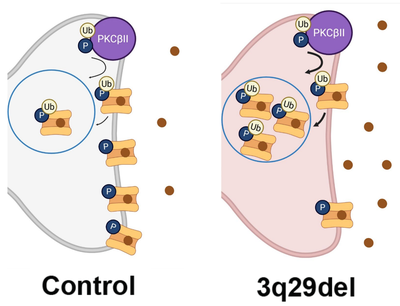
7 3q29del mice show attenuated locomotor response to amphetamine.



8 3q29del mice show blunted response to PKCβII inhibitor (LY333531).



Hypothesis PKCβII activity is elevated in 3q29del mice, causing excess internalized DAT.



Conclusions & Future Directions

- Altered PKCβII activity is driving dopamine transporter dysfunction in 3q29del mouse striatum.
- Localized injections of the PKCβII inhibitor LY333531 into the dorsal striatum to determine effects on dopamine levels, DAT activity, and locomotor behavior.

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