Revealing Neurogenetic Signatures: Machine Learning Uncovers Repetitive Behaviors in ASD and OCD Genetic Model Mice

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Background

Alterations in motor output are a common behavioral abnormality seen across multiple neurodevelopmental disorders (NDD). Here, we use machine-learning based classifiers to rigorously quantify behavioral structure in 3 NDD genetic models.

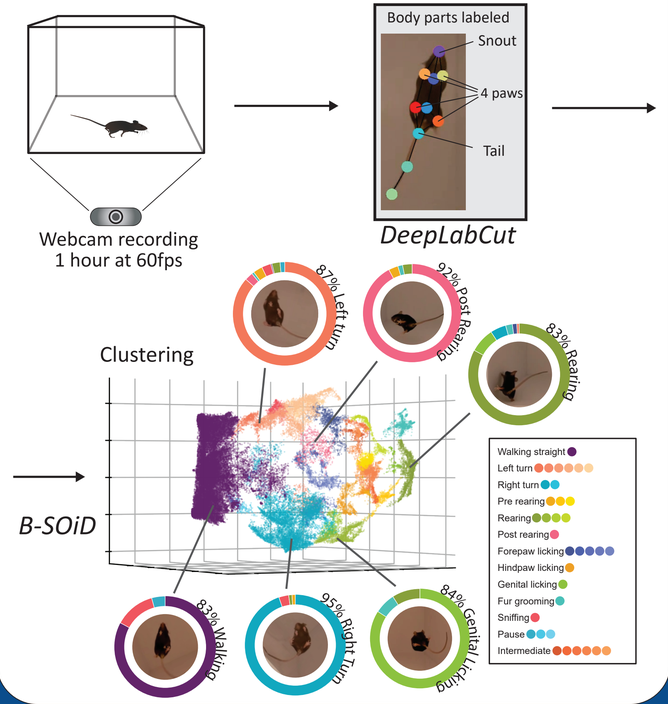
With the increasing focus on epigenetic dysregulation in the pathophysiology of autism spectrum disorder (ASD), we investigated the role of a candidate ASD gene that preliminarily shows a role in synaptic function. The Kmt2c gene, also known as Mll3, acts as a monomethyltransferase on histone 3 lysine residues, and is hypothesized to impact synapse-specific gene regulation.

Previous literature on the Neurexin1α loss-of-function has shown large effects on mouse behavior, although when Nrxn1 functions in mediating this is unclear. With the help of the Zhou lab, we investigated Nrxn1-Flex mice, wherein the null allele is initially expressed and can be reverted to the wildtype allele in the presence of Cre.

Lastly, we looked at the Slitrk5 gene, whose mutations are associated with obsessive compulsive disorder (OCD). Given that literature has shown Slitrk5 to be correlated with corticostriatal dysfunction, we screened for any repetitive behavior in mice.

Methods

Behavioral Analysis



Mll3 ASD model (TADA score: 17th)

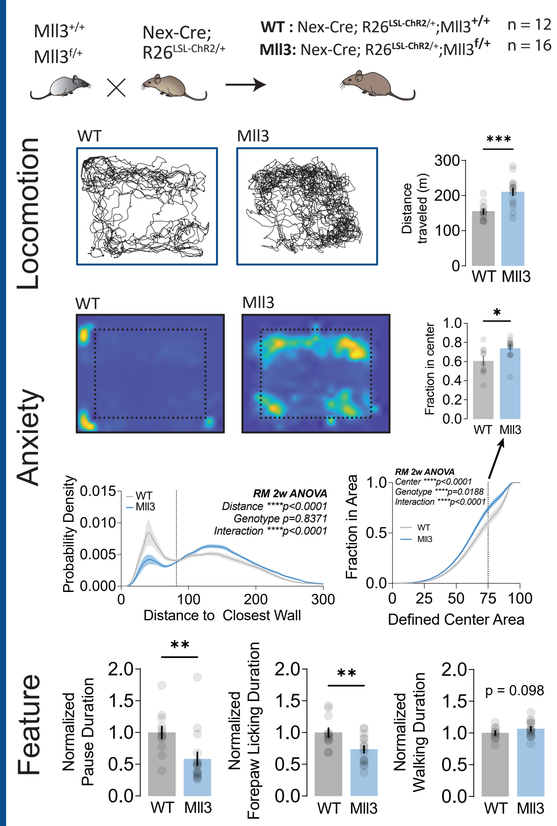


Figure 1. Mouse model of ASD using the Mll3 gene (A) Breeding strategy for WT and Mll3 Het mice for the Mll3 gene with channel rhodopsin 2 (B) Trajectories for representative mice of each genotype over a 1 hour period in an openfield setup with a graph of total distance travelled to compare overall locomotion (C) Heatmaps of trajectories of individual WT and Mll3 Het mice (D) Anxiety measures using a center area and distance to the closest wall to compare exploration of WT compared to Mll3 Het mice (E) Comparison of behaviors between WT and Mll3 Het mice normalized to WT population values

Nrxn1 ASD model (TADA score: 4th)

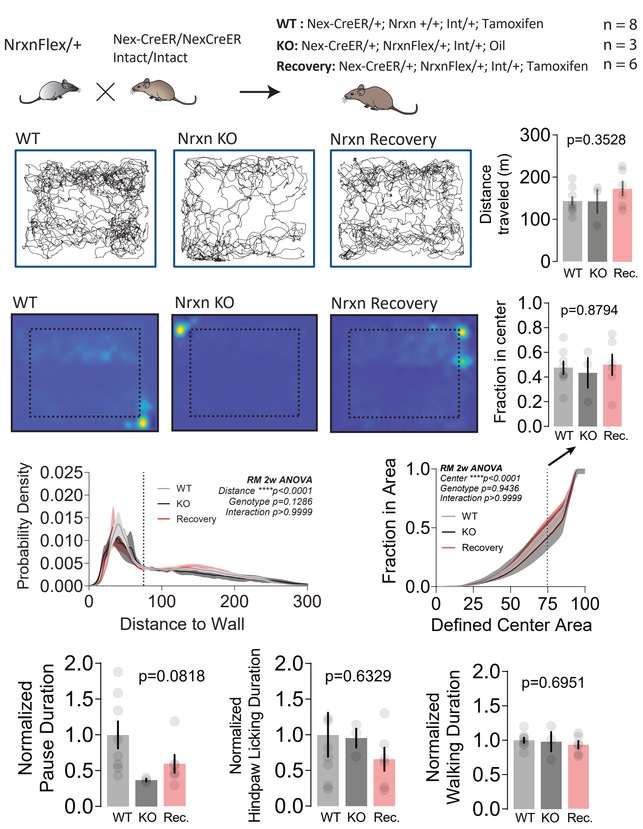


Figure 2. Mouse model of ASD using the Nrxn1 gene (A) Breeding strategy for WT, Het KO, and Recovery mice for the Nrxn1 gene (B) Trajectories for representative mice of each genotype over a 1 hour period in an openfield setup with a graph of total distance travelled to compare overall locomotion (C) Heatmaps of trajectories of individual WT, Het KO, and Recovery mice (D) Anxiety measures using a center area and distance to the closest wall to compare exploration of WT and Het KO to Recovery mice (E) Comparison of behaviors between WT, Het KO, and Recovery mice normalized to WT population values

Slitrk5 OCD model

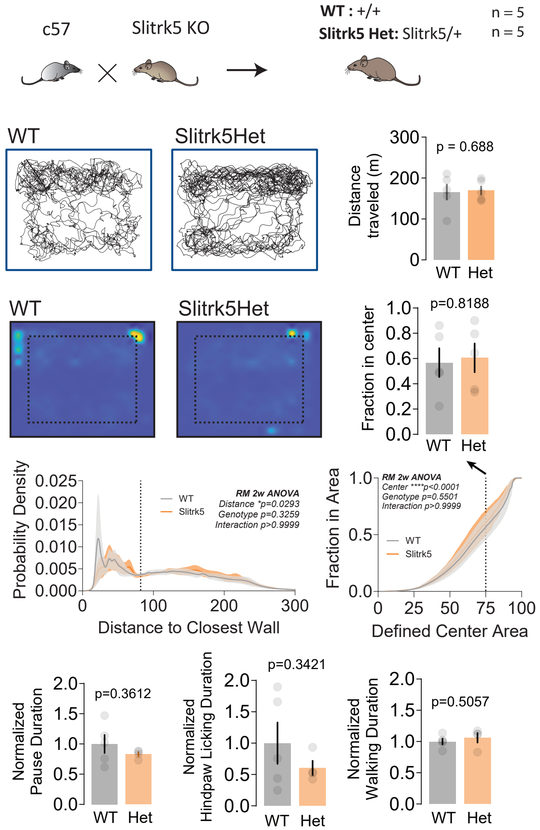


Figure 3. Mouse model of OCD using the Slitrk5 gene (A) Breeding strategy for WT and Het mice for the Slitrk5 gene (B) Trajectories for representative mice of each genotype over a 1 hour period in an openfield setup with a graph of total distance travelled to compare overall locomotion (C) Heatmaps of trajectories of individual WT and Het mice (D) Anxiety measures using a center area and distance to the closest wall to compare exploration of WT to Het mice (E) Comparison of behaviors between WT and Het mice normalized to WT population values

Conclusion

Mll3: significant locomotive difference between WT and Het animals. Het mice traveled more distance, spent more time in the center exploring the new environment, and notably performed less grooming behavior in the form of paw licking.

Nrxn1: no significant behavioral differences among the mice that we had run but have since run more cohorts. This evidence indicates that the recovery of the Nrxn1 gene presents a similar phenotype to WT animals, and with more mice we hope to see a difference between the KO phenotypes and WT and Recovery phenotypes.

Slitrk5: only 5 mice of each phenotype, so the preliminary data may not have enough power to display significant results. While there were no significant anxiety or behavioral differences between Het and WT mice, the data suggests that Het mice might perform some paw licking behavior less often.

References

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