

# Unraveling Social Responsiveness: A Comparison Between *SCN2A*, *GRIN2B*, and *SETBP1* Pathogenetic Variants

Presenters: R. Olivia Mace & Wae Man Chan

Co-Authors: Sophie Cramer-Benjamin, Ashlan R. Cheever, & Caitlin M. Hudac, Ph.D.  
Department of Psychology & Carolina Autism and Neurodevelopment (CAN) Research Center

## Background

- Pathogenetic variants to *SCN2A*, *GRIN2B*, and *SETBP1* genes are linked to a range of neurodevelopmental differences, including intellectual disability (ID) and autism spectrum disorder (ASD) (1,2,3,4)
- Social responsiveness** refers to an individual's ability to appropriately interpret and respond to social cues in interactions (5)
  - In the context of ASD, social responsiveness is often measured using standardized tools like the Social Responsiveness Scale, Second Edition (SRS-2) (6)
  - Impairments in social responsiveness are a key characteristic of ASD, and deficits can affect reciprocal communication, relationships, and social adaptive behavior (5)

## Objective

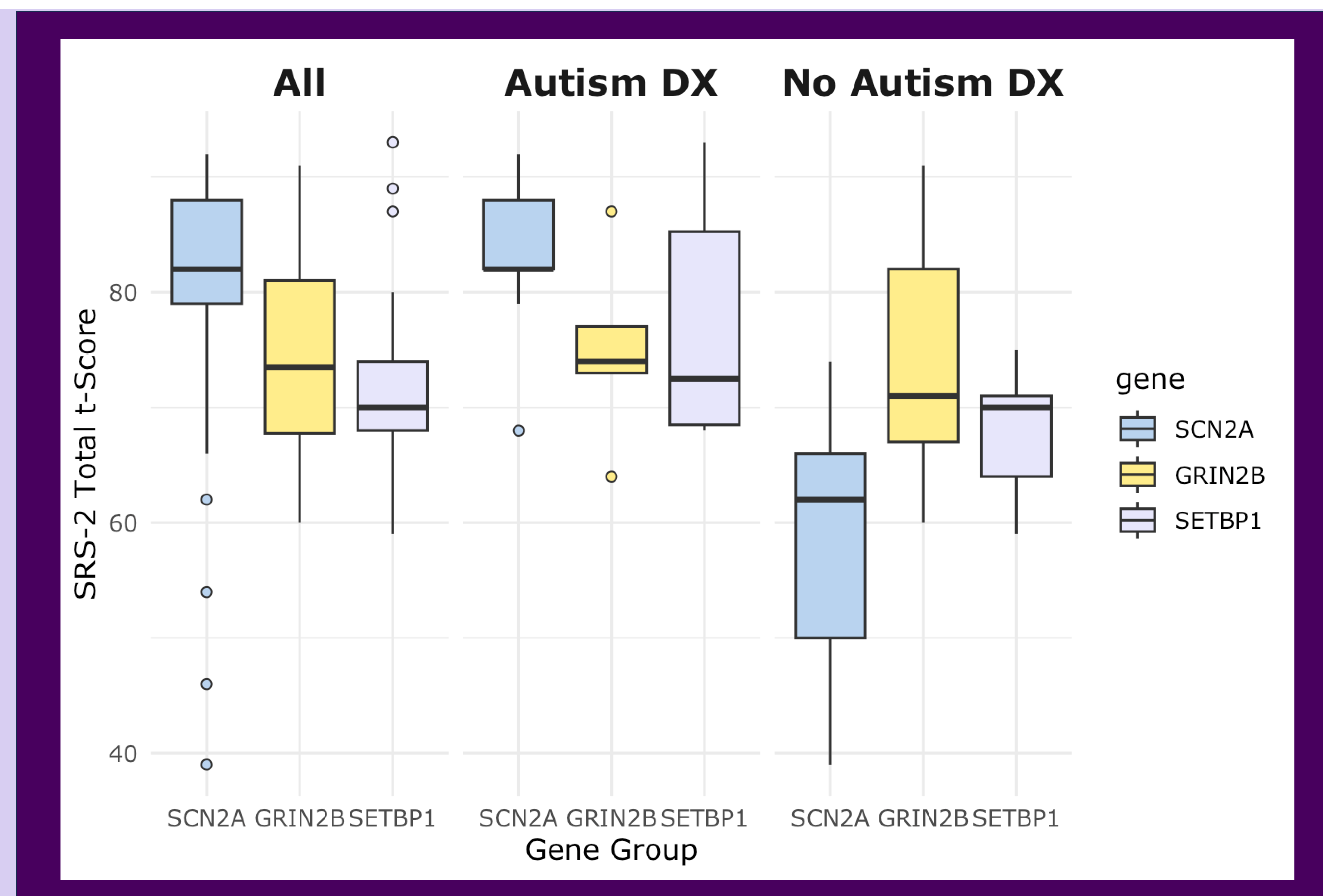
- Evaluate the distinct social responsiveness profiles associated with *SCN2A*, *GRIN2B*, and *SETBP1* variants
- Assess if autistic individuals within these gene groups exhibit significantly different social responsiveness profiles

## Methods

- 77 individuals across three genetic groups: *SCN2A*, *GRIN2B*, and *SETBP1*
- Social Responsiveness Scale, Second Edition (SRS-2) was used to evaluate their social responsiveness (6)

## Participant Information

Gene Group	N (% autistic)	Age M (SD)
<i>SCN2A</i>	36 (80.6%)	9 (4.42)
<i>GRIN2B</i>	18 (27.8%)	9.5 (6.20)
<i>SETBP1</i>	23 (43.5%)	12 (8.80)



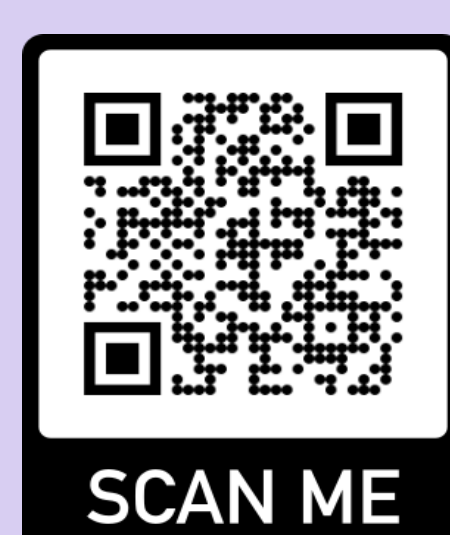
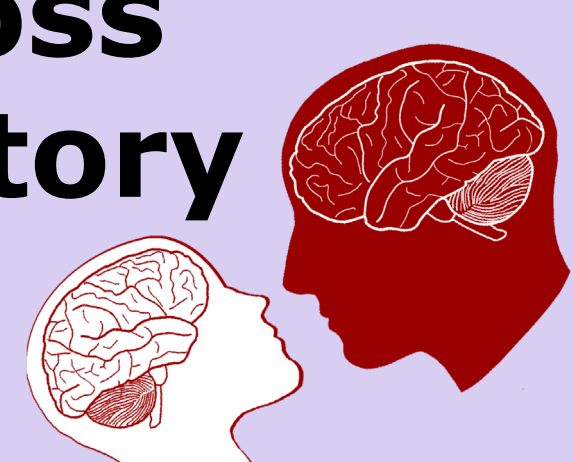
**Figure 1. Boxplot.** A mixed effects ANOVA,  $F(2, 74)=3.89$ ,  $p=0.025$ , indicated a significant difference in social responsiveness between groups.

- Fischer's LSD post-hoc test indicated that *SCN2A* group had elevated social responsiveness concerns relative to *SETBP1* group ( $p=0.009$ ) but no other groups differed ( $p>.05$ ).

A linear mixed effects model was fit to examine the effects of autism diagnosis on social responsiveness in each gene group. This interaction effect explains 56% of the variability in the social responsiveness score,  $F(5, 71)=18.09$ ,  $p<.0001$ . Autistic people in the *SCN2A* group had significantly higher t-scores than non-autistic people in *SCN2A* group, ( $\beta =-25.55$ ,  $\sigma =5.17$ ,  $t=-4.93$ ,  $p<.0001$ ). No other interactions were observed.

## MAIN TAKEAWAYS

- Genetic factors contribute to ASD-related social differences, reinforcing the need for gene-specific research.
- Individuals with *SCN2A*-related ASD exhibit significantly elevated social responsiveness concerns, indicating more severe social difficulties compared to established clinical thresholds.
- Future approaches could consider observational methods rather than parent-report alone, as well as tailored therapeutic approaches focusing on social skills training



### References:

- Platzer, K., Yuan, H., Schütz, H., Winschel, A., Chen, W., Hu, C., Kusumoto, H., Heyne, H. O., Helbig, K. L., Tang, S., Willing, M. C., Tinkle, B. T., Adams, D. J., Depienne, C., Keren, B., Mignot, C., Frengen, E., Strömme, P., Biskup, S., Döcker, D., ... Lemke, J. R. (2017). GRIN2B encephalopathy: novel findings on phenotype, variant clustering, functional consequences and treatment aspects.
- Platzer, K., & Lemke, J. (2021, March 25). GRIN2B-related neurodevelopmental disorder.
- Schwarz, N., Hahn, A., Bast, T., Müller, S., Löffler, H., Maljevic, S., Gaily, E., Prehl, I., Biskup, S., Joensuu, T., Lehesjoki, A.-E., Neubauer, B. A., Lerche, H., & Hedrich, U. B. S. (2016). Mutations in the sodium channel gene SCN2A cause neonatal epilepsy with late-onset episodic ataxia.
- Oyler, H. O., Hudac, C. M., Chung, W. K., Green Synder, L., Robertson, S., Srivastava, S., & Geyer, T. (2024). SETBP1 haploinsufficiency and related disorders clinical and neurobehavioral phenotype study.
- Constantino, J., & Gruber, J. (2005). Social Responsiveness Scale (SRS) Manual.
- Constantino, J. N., & Gruber, C. P. (2012). Social Responsiveness Scale-Second Edition (SRS-2).