Variability in externalizing behavior problems among individuals with ASD-associated disruptive mutations

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INTRODUCTION

- Externalizing behavior problems are elevated in ASD, but the biological and genetic mechanisms that influence externalizing severity in ASD are not well understood (Bauminger et al., 2010; Ibrahim et al., 2019; Lundwall et al., 2017)
- Case series have noted elevated externalizing problems among individuals with mutations in specific ASD-associated genes (e.g., Siper et al., 2017), but rates and predictors of externalizing behavior have not been systematically reported or compared across gene groups
- Individuals with mutations in ASD-associated genes may exhibit risk factors for increased externalizing behavior, such as elevated ASD symptoms, adaptive behavior deficits, and gastrointestinal problems (Beighley et al., 2019; Hartley et al., 2008; Jang et al., 2011; Kurtz-Nelson et al., 2020; Neuhaus et al., 2018)
- The goal of this study was to examine externalizing problem severity across ASD-associated gene groups after controlling for demographic, clinical and medical factors associated with externalizing problems in ASD

METHOD

- 196 individuals (mean age = 7.25 years, 51% female) with a disruptive mutation to one of 14 ASD-associated genes were drawn from an ongoing genetics-first study at the University of Washington (TIGER) and from the Simons Variation in Individuals Project (Simons VIP Consortium, 2012)

Measures:

- Child Behavior Checklist, Externalizing T-score (Achenbach & Rescorla, 2001)
- Vineland-II or Vineland-III (Sparrow et al., 2005; Sparrow et al., 2016), the Social Responsiveness Scale-II (Constantino & Gruber, 2012)
- Medical history interview

- One-way ANOVA conducted to compare externalizing severity across gene groups; one-way ANCOVA conducted to determine whether cross-gene differences remained significant after controlling for age, adaptive behavior, ASD symptom severity, and GI problems (severe constipation or diarrhea).

RESULT

- Externalizing severity significantly differed across gene groups, $F(13, 182) = 4.20$, $p < .001$
- Remained significant after controlling for ASD symptom severity, adaptive behavior, age, and GI problems, $F(13, 113) = 2.68$, $p = .003$

When compared to individuals with mutations to other ASD-associated genes and after controlling for age, adaptive behavior, ASD symptom severity, and GI problems, externalizing behavior problems are:

- **Elevated** in *ADNP* and *FOXP1*
- **Reduced** in *PACS1*

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- ASD symptom severity was significantly associated with externalizing severity, $F(1, 113) = 26.27$, $p < .001$; age, adaptive behavior, and GI problems were not associated
- Post hoc comparisons (Bonferroni correction applied) indicated cross-gene differences driven by high externalizing in *ADNP* and *FOXP1* and by low externalizing in *PACS1*

CBCL Externalizing T-Scores across Genetic Mutation Groups

Gene	*N*	*M (SD)*	% in Clinical Range
ADNP	15	66.33 (9.01)	60.00
ARID1B	5	48.60 (8.11)	0.00
ASXL3	10	57.50 (9.68)	30.00
CHD8	12	51.25 (8.71)	16.67
CSNK2A1	5	52.20 (11.58)	20.00
DYRK1A	19	56.79 (11.41)	21.05
FOXP1	5	72.60 (2.88)	100.00
GRIN2B	25	53.88 (7.70)	12.00
MED13L	7	53.43 (9.03)	14.29
PACS1	15	51.67 (11.54)	13.33
PPP2R5D	18	50.83 (13.05)	16.67
SCN2A	40	50.75 (12.71)	22.50
STXBP1	13	48.92 (8.13)	0.00
SYNGAP1	7	62.00 (6.00)	42.86

DISCUSSION

- Externalizing problem severity varies significantly across ASD-associated mutation groups
- Elevated externalizing problems in *FOXP1* consistent with recurrent case reports of clinically significant aggression and mood lability (Hamdan et al., 2010; Sollis et al., 2016)
- Tantrums and aggression reported in majority of published *ADNP* cases, (Van Dijck et al., 2019), with some reports of severe disruptive behavior (Shillington et al., 2020)
- Externalizing problems may be characteristic of *ADNP* and *FOXP1* haploinsufficiency, but additional research needed on mechanisms, topography, and function
- Behavior problems commonly reported in *PACS1* case series (Schuurs-Hoejimakers et al., 2016), but not elevated when compared to other individuals with ASD-associated mutations, highlighting the importance of cross-gene comparisons