Journal of Autism and Developmental Disorders (2021) 51:3365–3373
https://doi.org/10.1007/s10803-020-04774-z

BRIEF REPORT

# Brief Report: Associations Between Self-injurious Behaviors and Abdominal Pain Among Individuals with ASD-Associated Disruptive Mutations

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Accepted: 27 October 2020 / Published online: 11 November 2020


## Abstract

Self-injurious behaviors (SIB) are elevated in autism spectrum disorder (ASD) and related genetic disorders, but the genetic and biological mechanisms that contribute to SIB in ASD are poorly understood. This study examined rates and predictors of SIB in 112 individuals with disruptive mutations to ASD-risk genes. Current SIB were reported in 30% of participants and associated with poorer cognitive and adaptive skills. History of severe abdominal pain predicted higher rates of SIB and SIB severity after controlling for age and adaptive behavior; individuals with a history of severe abdominal pain were eight times more likely to exhibit SIB than those with no history. Future research is needed to examine associations between genetic risk, pain, and SIB in this population.

**Keywords** Autism spectrum disorder · Intellectual disability · Rare genetic disorders · Self-injurious behavior · Abdominal pain

## Introduction

Self-injurious behaviors (SIB), defined as self-directed behaviors with the potential to cause tissue damage, are clinically concerning for individuals with autism spectrum disorder (ASD) and for their caregivers and providers (Minshawi et al. 2015; Oliver and Richards 2015). SIB prevalence is elevated in ASD as compared to other developmental disabilities, and population-based prevalence of SIB among children with ASD in the United States has been estimated at 28% (McClintock et al. 2003; Soke et al. 2016). SIB in ASD are associated with key negative outcomes, including significant functional impairment, restricted access to community settings, caregiver stress, higher health care utilization, and increased risk of life-threatening injury (Gulsrud et al. 2018; Kalb et al. 2012; Minshawi et al. 2015; Rattaz et al. 2015). SIB often persist over time, and well-established SIB may be more resistant to treatment (Minshawi et al. 2015; Oliver and Richards 2015). While interventions to prevent SIB have been proposed for over a decade (e.g., Richman 2008), efforts are hampered by an incomplete understanding of the mechanisms that contribute to SIB and the risk factors for SIB in ASD, thereby limiting the development of targeted interventions (Dempsey et al. 2016; Dimian et al. 2017; Minshawi et al. 2015; Shirley et al. 2016).

A leading hypothesis regarding one mechanism of SIB, the pain-related hypothesis, proposes that SIB may express or alleviate pain related to medical conditions (Minshawi et al. 2015; Peebles and Price 2012; Symons 2011). Operant models further suggest SIB that emerged as a response to painful medical conditions (e.g., gastrointestinal pain)

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s10803-020-04774-z) contains supplementary material, which is available to authorized users.

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may later be maintained by social and environmental contingencies (e.g., social attention or escape from demands; Oliver and Richards 2015). Genetic mechanisms are also proposed to increase risk for SIB (Huisman et al. 2018), and ASD-associated developmental disorders caused by single gene mutations, including Fragile X syndrome and Cornelia de Lange syndrome, have been previously associated with elevated SIB (Arron et al. 2011; Moss et al. 2008; Symons et al. 2003; Wolff et al. 2012). Pain or discomfort due to syndrome-related health conditions, particularly gastrointestinal conditions, may specifically contribute to SIB in genetic disorders; for example, gastroesophageal reflux is associated with SIB in Cornelia de Lange syndrome (Luzzani et al. 2003). Individuals with ASD-associated genetic disorders often exhibit risk factors for SIB, such as severe intellectual disability, language impairment, and elevated ASD symptoms; these factors are proposed to increase the likelihood that early, self-stimulating repetitive behaviors will emerge and develop into SIB due to automatic and social reinforcement (Oliver and Richards 2015; Rojahn et al. 2016). As such, syndrome-related health conditions (e.g., gastrointestinal problems) and early developmental risk factors (e.g., severe communication impairment) may interact or combine to promote SIB in genetic disorders associated with ASD.

Gastrointestinal (GI) pathology affects up to 37.4% of children with ASD, with greater prevalence and severity as compared to typically developing children (Chandler et al. 2013; Fulceri et al. 2016; Mazurek et al. 2013; McElhanon et al. 2014; Molloy and Manning-Courtney 2003). Commonly reported symptoms include chronic constipation, abdominal pain, diarrhea, and gastroesophageal reflux disease. Importantly, there is high correlation between GI symptoms and behavioral traits in ASD. Children with both ASD and GI problems have higher levels of anxiety, externalizing symptoms, and irritability (Chaidez et al. 2014; Fulceri et al. 2016; Mazurek et al. 2014). In a recent study, GI problems predicted SIB for young children with ASD after controlling for severity of ASD symptoms, adaptive behavior, cognitive skills, and family income (Neuhaus et al. 2018). Given the complex neurodevelopmental disabilities in ASD, unrecognized and untreated abdominal pain and GI symptoms pose a burden that may compound upon existing neuropsychiatric deficits.

In recent years, novel disruptive single gene mutations have been identified and strongly associated with ASD through large-scale exome sequencing efforts in large ASD cohorts (Iossifov et al. 2014; O'Roak et al. 2012). Phenotypes associated with mutations in specific genes appear to differ across gene groups (Beighley et al. 2020; Earl et al. 2017). Individuals with mutations in rare ASD-associated genes may share common risk for co-occurring health problems, particularly GI problems (e.g., constipation in *CHD8* and gastroesophageal reflux disease in *DYRK1A*; Bernier et al. 2014; Kurtz-Nelson et al. 2020). A causal relationship between genetic risk and impacted gut functioning has been proposed in specific mutation groups, particularly *CHD8* (Bernier et al. 2014). Despite elevated health problems, the nature and prevalence of the pain experience in this population is currently unknown. SIB has been reported in individuals with ASD-associated mutations (e.g., *ADNP* and *FOXP1*; Siper et al. 2017; Van Dijck et al. 2019), but the prevalence and correlates of SIB across gene groups have not been systematically assessed. As such, the primary aim of this study was to examine and compare rates of SIB and history of abdominal pain across mutation groups. The secondary aim was to examine abdominal pain as a predictor of SIB. We hypothesized that a history of severe abdominal pain would be associated with SIB status and SIB severity after controlling for age and adaptive behavior.

## Methods

### Participants

Participants included 112 individuals (ages 24 months to 21 years) who were assessed as part of an ongoing study examining the phenotype of individuals ascertained based on the presence of a disruptive mutation to ASD associated risk genes (Table 1). Participants with previously identified mutations to ASD-associated genes were recruited from multiple sources, including genetic studies that allowed for participant recontact and rare disorder family groups.

**Table 1** Demographic and clinical participant characteristics (N = 112)

| Demographic | *n* | % | *M* | *SD* |
|---|---|---|---|---|
| Gender (*n* = 112) | | | | |
| Female | 54 | 48.2 | | |
| Male | 58 | 51.8 | | |
| ASD diagnosis (*n* = 108) | 77 | 71.3 | | |
| GDD/ID diagnosis (*n* = 112) | 99 | 88.4 | | |
| Age in months (*n* = 112) | | | 105.33 | 56.75 |
| Full-scale IQ (*n* = 89) | | | 44.10 | 23.87 |
| VABS-II composite (*n* = 107) | | | 54.36 | 14.44 |
| VABS-II communication (*n* = 107) | | | 55.77 | 16.86 |
| Self-injurious behaviors (SIB; *n* = 91) | 27 | 29.7 | | |
| Severe abdominal pain (*n* = 107) | 19 | 17.8 | | |
| RBS-R self-injury subscale score (*n* = 104) | | | 3.31 | 3.50 |
| SRS-2 total T scores (*n* = 99) | | | 78.24 | 10.82 |

*ASD* autism spectrum disorder, *GDD* global developmental delay, *ID* intellectual disability, *RBS-R* Repetitive Behavior Scale, Revised, *SRS-2* Social Responsiveness Scale, Second Edition, *VABS-II* Vineland Adaptive Behavior Scale, Second Edition

Genetic findings (clinical genetic testing reports or results of previous research sequencing) were reviewed by a geneticist to confirm the presence of a pathogenic or likely pathogenic mutation in one of eight high confidence ASD risk genes (*ADNP, ARID1B, CHD8, CTNNB1, DYRK1A, FOXP1, GRIN2B, SCN2A*; Stessman et al. 2017). Gene, variant, mutation effect, and inheritance information for participants are listed in Supplemental Table 1. Informed consent was obtained from all participating caregivers, and consent or assent was obtained from participants who were capable of providing consent or assent.

## Measures

Primary caregivers completed structured and comprehensive medical and psychiatric history interviews adapted from the Simons Simplex Collection (Fischbach and Lord 2010). Participants also completed a standardized battery of clinical and diagnostic assessments. Using all available information, psychiatric diagnoses were confirmed or newly provided by a licensed psychologist using the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (American Psychiatric Association 2013). All assessments were conducted by experienced clinicians with expertise in neurodevelopmental disorders who at the time of assessment were naïve to the type of disruptive mutation.

### Abdominal Pain

The presence of severe abdominal pain was coded based on caregiver report of a past or current diagnosis from a medical professional during the medical history interview. Individuals with past but not current abdominal pain were coded here per the revised operant model of SIB, which proposes that SIB which initially emerge as a response to pain may later be maintained by other contingencies after painful health conditions have resolved (Oliver and Richards 2015). Additional specifiers, including the age of onset, whether pain was resolved or unresolved, and whether pain presented as chronic (continuous/frequent) or intermittent (occasional) when present were used to further characterize severe abdominal pain.

### Cognitive and Adaptive Functioning

Participant full-scale IQ (FSIQ) was assessed using the *Mullen Scales of Early Learning* (Mullen 1995), *Differential Abilities Scale, 2nd Edition* (Elliott 2007), or *Wechsler Abbreviated Scale of Intelligence, 2nd Edition* (Wechsler 2011) depending on age and developmental level. IQ scores were generated using deviation scores (standard; $M = 100$, $SD = 15$) or ratio scores (mental age equivalent/chronological age $\times$ 100) if standard scores could not be calculated.

To measure adaptive functioning, caregivers were administered the *Vineland Adaptive Behavior Scales, 2nd edition* (VABS-2; Sparrow et al. 2005). An overall score (Adaptive Behavior Composite) and a Communication subscale score were generated ($M = 100$, $SD = 15$).

### ASD-Specific Assessment

Research-reliable clinicians administered the *Autism Diagnostic Interview-Revised* (ADI-R; Rutter et al. 2003) and the appropriate module of the *Autism Diagnostic Observation Schedule, Second Edition* (ADOS-2; Lord et al. 2013). Parents also completed the *Social Responsiveness Scale, Second Edition* (SRS-2; Constantino and Gruber 2012), from which standardized $T$ scores ($M = 50$, $SD = 10$) were generated. ADOS-2 comparison scores (1–10 possible range, higher scores indicating greater severity) and SRS-2 scores were used as measures of ASD symptom severity.

### Self-injurious Behaviors (SIB)

A dichotomous variable for the presence or absence of current SIB was created from item 83 of the ADI-R using procedures described by Dempsey et al. (2016). Individuals with a score of 2 (SIB definitely present, $n = 27$) or 3 (SIB definitely present and severe, $n = 0$) were coded as engaging in current SIB, individuals with a score of 0 (SIB not present, $n = 64$) were coded as not engaging in SIB. Individuals with a score of 1 (possible or mild SIB, $n = 21$) were excluded from all analyses involving the ADI-R. While the ADI-R is frequently used as a measure of current SIB prevalence, scores of 1 have not been consistently coded as present or absent SIB across studies (Duerden et al. 2012; Gulsrud et al. 2018; Soke et al. 2018); they were excluded following procedures established by previous researchers (Dempsey et al. 2016; Kanne and Mazurek 2011). The proportion of participants with a score of 1 did not significantly differ across gene groups per Fisher's exact test, $p = .28$. For consistency with other measures of current behavior and to establish a temporal relation with history of abdominal pain (i.e., abdominal pain occurring prior to or concurrent with SIB), individuals with past but not current SIB were not coded here. Parents also completed the *Repetitive Behavior Scale-Revised* (RBS-R; Bodfish et al. 2000), and the self-injury subscale score (0–24 possible range) was used as a continuous measure of current SIB severity.

## Data Analyses

Analyses were completed in SPSS version 23. Descriptive analyses of demographic and clinical factors (age, sex, diagnoses, FSIQ, adaptive behavior, ASD symptoms, SIB, and abdominal pain) were performed on the whole sample. To

address the primary aim, Fisher's exact test with two-sided Monte Carlo significance estimates (samples = 10,000, starting seed = 2,000,000) was used to determine whether rates of SIB and severe abdominal pain differed significantly across gene groups. One-way ANOVA was used to determine whether SIB severity differed significantly across gene groups. To address the secondary aim, T-tests, Fisher's exact test, and bivariate correlations were used to examine associations between SIB or abdominal pain and demographic variables (age, sex, FSIQ, adaptive behavior, ASD symptoms) as well as associations between SIB and abdominal pain specifiers (resolved vs. unresolved, intermittent vs. chronic, age of onset). Binary logistic regression was used to determine whether history of severe abdominal pain predicted SIB status (dichotomous variable measured by ADI-R) after controlling for age and adaptive behavior, while linear regression was used to determine whether history of severe abdominal pain predicted SIB severity (continuous variable measured by RBS-R) after controlling for age and adaptive behavior. Age was selected as a control variable due to the wide age range in the study and previous associations between SIB and age (e.g., Gulsrud et al. 2018). Adaptive behavior was selected as an indicator of general developmental functioning; it was used in analyses instead of IQ as it was highly correlated with IQ ($r(87) = .75$, $p < .001$), previously associated with SIB in ASD (Neuhaus et al. 2018), and available for more participants.

## Results

### Self-injurious Behaviors

Across gene groups, the prevalence of current SIB (excluding participants with possible or mild SIB) ranged from 55.6% (*GRIN2B*) to 0.0% (*ARID1B, FOXP1*); however, SIB prevalence did not differ across gene groups ($p = .20$), nor did SIB severity ($F(7,96) = 1.37$, $p = .23$, $\eta_p^2 = .09$). Individuals with SIB had lower adaptive behavior ($t(84) = 2.37$, $p = .02$, $d = 0.57$), lower communication skills ($t(84) = 2.42$, $p = .02$, $d = 0.60$) and lower IQ ($t(69) = 2.13$, $p = .04$, $d = 0.61$) than those with no current SIB. Differences in ASD symptom severity as measured by the SRS-2 ($t(78) = -1.96$, $p = .05$, $d = 0.52$) and ADOS-2 comparison score ($t(73) = -1.98$, $p = .05$, $d = 0.53$) did not reach significance. Sex ($p = .65$) and age ($t(89) = 0.18$, $p = .86$, $d = 0.04$) were not associated with SIB prevalence. Increased SIB severity was significantly associated with lower adaptive behavior ($r(101) = -.20$, $p = .04$) and increased ASD symptom severity as measured by the SRS-2 ($r(98) = .32$, $p = .001$). SIB severity was not associated with IQ ($r(83) = -.13$, $p = .24$), communication skills ($r(101) = -.19$, $p = .07$), ADOS-2 comparison score ($r(89) = .03$, $p = .77$), sex ($t(102) = 1.26$, $p = .21$, $d = 0.25$), or age ($r(104) = .04$, $p = .71$).

### Abdominal Pain

Prevalence of lifetime severe abdominal pain ranged from 35.3% (*ADNP*) to 0.0% (*ARID1B, FOXP1*) across gene groups, but did not differ across groups ($p = .24$). History of severe abdominal pain was not associated with adaptive behavior ($t(101) = 0.86$, $p = .39$, $d = 0.19$), communication skills ($t(101) = 0.69$, $p = .49$, $d = 0.16$), IQ ($t(85) = 0.43$, $p = .67$, $d = 0.12$), ASD symptom severity as measured by the SRS-2 ($t(94) = -1.66$, $p = .10$, $d = 0.49$), ASD symptom severity as measured by the ADOS-2 ($t(89) = 0.19$, $p = .85$, $d = 0.05$), sex ($p = .81$), or age ($t(105) = -1.01$, $p = .32$, $d = 0.24$). Among individuals with a history of severe abdominal pain, abdominal pain was described as unresolved in 63.2% and as chronic in 57.9%. SIB prevalence and severity did not differ between individuals with resolved versus unresolved abdominal pain (prevalence: $p > .99$; severity: $t(17) = -0.49$, $p = .63$, $d = 0.22$) or between individuals with chronic versus intermittent abdominal pain (prevalence: $p = .52$; severity: $t(16) = 0.15$, $p = .88$, $d = .07$). Age of abdominal pain onset was also not associated with SIB severity ($r(19) = -.29$, $p = .23$) or prevalence ($t(13) = 1.51$, $p = .16$, $d = 0.77$).

### SIB and Abdominal Pain

Results of the binary logistic regression predicting SIB status from adaptive behavior, age, and history of severe abdominal pain are presented in Table 2. This analysis included all participants with scores of 0, 2, or 3 on the ADI-R SIB item and with complete data for adaptive behavior and abdominal pain ($n = 83$); participants with a score of 1 on the ADI-R SIB item were excluded from analyses as described earlier. The final model correctly classified 77.1% of cases, with sensitivity of 38.5% and specificity of 94.7% (cutoff = .50). Adaptive behavior and severe abdominal pain both significantly contributed to the final model, with lower adaptive behavior ($p = .004$) and history of severe abdominal pain ($p = .003$) predicting increased likelihood of SIB. Participants with a history of severe abdominal pain were 8.08 times more likely to exhibit SIB than participants with no history; an odds ratio of 8.08 indicates a large effect size (Chen et al. 2010).

Results of the linear regression predicting SIB severity from adaptive behavior, age, and history of severe abdominal pain are presented in Table 3. This analysis included all participants with complete data for SIB severity (RBS-R), adaptive behavior, and abdominal pain ($n = 97$). Lower adaptive behavior ($p = .04$) and history of severe abdominal pain ($p = .01$) were significantly associated with increased SIB

**Table 2** Logistic regression model predicting presence of SIB

| Predictor | SIB status | | | | | |
|---|---|---|---|---|---|---|
| | Step 1 | | | Step 2 | | |
| | *B* | *SE B* | *Exp*(*B*) | *B* | *SE B* | *Exp*(*B*) |
| Age | − 0.01 | .01 | .99 | − .01 | .01 | .99 |
| Adaptive behavior | − .06** | .02 | .94 | − .07** | .02 | .94 |
| Severe abdominal pain | | | | 2.09** | .69 | 8.08 |
| Constant | 3.17 | 1.41 | 23.72 | 3.05 | 1.48 | 21.00 |
| $\chi^2$ | 9.69** | | | 19.96*** | | |

SIB status was coded as 1 for *yes* and 0 for *no* according to procedures described in Dempsey et al. (2016)
**$p < .01$. ***$p < .001$

**Table 3** Linear regression model predicting severity of SIB

| β | SIB severity | |
|---|---|---|
| | Step 1 | Step 2 |
| Age | − .05 | − .07 |
| Adaptive behavior | − .23* | − .22* |
| Severe abdominal pain | | .25* |
| $\Delta R^2$ | .05 | .06* |
| Final $R^2$ | | .11* |
| Final *F* | | 3.81* |

*$p < .05$

severity. To confirm consistency with the logistic regression predicting SIB status, this analysis was repeated excluding participants with a score of 1 on the ADI-R SIB item; the subsample consisted of all participants with scores of 0, 2, or 3 on the ADI-R SIB item and with complete data for SIB severity, adaptive behavior, and abdominal pain ($n = 75$). Results of this analysis are presented in Table S3. When participants with possible/unclear SIB per the ADI-R were excluded, only history of severe abdominal pain contributed to the final model predicting SIB severity ($p = .008$).

Given this strong association between severe abdominal pain and SIB, it was hypothesized that SIB could serve to express pain specifically for individuals with limited communication skills (Minshawi et al. 2015). As such, three exploratory analyses were conducted to determine whether communication skills moderated the identified relationships between severe abdominal pain and SIB status and severity. As described earlier, binary logistic regression was used to predict SIB status, and linear regression was used to predict SIB severity. The analysis predicting SIB severity was again repeated excluding participants with a score of 1 on the ADI-R SIB item. For all three exploratory analyses, history of severe abdominal pain and communication skills (centered at the mean) were entered in Step 1, and the interaction term was entered in Step 2. The samples used for the previous regressions predicting SIB status ($n = 83$), SIB severity ($n = 97$), and SIB severity excluding participants with possible/unclear SIB ($n = 75$) were also used for these exploratory analyses. Results of these analyses are presented in Tables S4, S5, and S6. Communication skills were independently associated with SIB status in the first step of the equation predicting SIB status ($p = .007$), but communication skills and the interaction between history of severe abdominal pain and communication skills were not associated with SIB prevalence or severity in any of the final models.

### SIB Topography

A post-hoc descriptive review of RBS-R SIB items was conducted to provide preliminary information about SIB topography in this sample. When examining RBS-R scores for all participants with a history of severe abdominal pain ($n = 19$), multiple topographies of SIB were endorsed by the majority of participants (68.4%); hitting self with body part, biting self, pulling hair or skin, and inserting finger or object into self were endorsed by over half of these participants. When this subsample was restricted to only participants with a history of abdominal pain and clear current SIB per the ADI-R ($n = 10$), 90.0% reported multiple SIB topographies. Finally, multiple SIB topographies were reported for 93.3% of participants with clear current SIB but no history of abdominal pain ($n = 15$). Biting self was the most commonly endorsed topography for this subsample, as well as the only topography endorsed by more than half of the subsample (87%).

## Discussion

History of severe abdominal pain was associated with SIB status and severity in a cohort of 112 individuals with disruptive mutations to ASD-associated genes. Most notably, history of severe abdominal pain (including resolved and unresolved pain) was strongly related to increased SIB risk after controlling for age and adaptive behavior. Severe abdominal pain was not associated with

other factors examined in this study (age, sex, IQ, adaptive skills, communication skills, or ASD symptoms), indicating that the association between SIB and abdominal pain was not explained by one of these factors. Communication skills did not moderate the relationship between severe abdominal pain and SIB, suggesting that this association does not uniquely apply to individuals with severely limited communication abilities. These findings are broadly consistent with pain-related models of SIB, which suggest that painful health conditions may contribute to the development and persistence of SIB. This study presents the first demonstration of that hypothesis in a sample of individuals with rare disruptive mutations to ASD-associated genes, who are at elevated risk for complex and co-occurring developmental and medical problems (Kurtz-Nelson et al. 2020). For these individuals, associations between genetic risk and SIB may be mediated or moderated by pain experience.

To the best of our knowledge, this is the first study to examine the prevalence and predictors of SIB among individuals with rare mutations to high-confidence ASD-risk genes. Thirty percent of participants exhibited current SIB, which is consistent with reported SIB prevalence among individuals with ASD and no known genetic cause (Gulsrud et al. 2018; Soke et al. 2016). SIB status was associated with adaptive behavior across gene groups and was not clearly associated with severity of ASD symptomatology, which is also consistent with recent findings (Gulsrud et al. 2018). These results suggest that similar mechanisms could predict SIB among individuals with known or unknown genetic risk for ASD. The prevalence of SIB across gene groups ranged from 55.6 to 0.0%, but these differences were not significant. While this finding may be due to small sample sizes across gene groups, it could alternately indicate that SIB among individuals with ASD-associated mutations is better explained by shared risk factors across groups—i.e., medical comorbidities or intellectual disability—as opposed to the unique effects of specific mutations. Additional phenotyping of individuals with these rare events is needed to understand whether certain gene groups may be at increased risk for SIB.

The mechanisms driving abdominal pain among individuals with rare ASD-risk mutations are unclear and require further exploration. Individuals with ASD-associated mutations could be at risk of an impacted gut-brain axis due to genetic and biological factors that may also underlie ASD. Other potential etiologies may contribute to higher GI symptoms in children with ASD and associated mutations, including neuropeptide imbalances, adverse effects of medications, and delay in identification and treatment of precipitating factors for abdominal pain (e.g., constipation and feeding concerns; Kong et al. 2019; Samsam et al. 2014). Additional research is needed to understand contributors to abdominal pain among individuals with rare ASD-associated mutations.

Results of this study also highlight the need for further research on pain assessment and treatment among individuals with ASD-associated disruptive mutations. Poorly treated or untreated pain can contribute to a cycle of maladaptive behaviors, and identification and treatment of pain symptoms may improve quality of life for individuals with ASD and their caregivers. The American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition have called for additional research in this area (Coury et al. 2012). Key areas for future investigation include testing available measures for pain assessment and developing screening tools for clinical settings. Given their complex and variable medical needs, individuals with ASD-associated mutations may benefit from a personalized medicine approach that includes individualized pain assessment and treatment.

Findings of this study should be interpreted in light of several limitations. First, this is a small sample in which complete data were not available for all measures; in some instances, participants did not complete all measures or valid scores could not be generated for a measure (e.g., ADOS-2 comparison scores for participants with severe mobility and sensory impairments). In addition, this sample reported a lower rate of severe abdominal pain (18%) in comparison to community sample reports of abdominal pain in up to one third of children (Chitkara et al. 2005; Saps et al. 2009). The rate of reported abdominal pain in this sample may reflect the high prevalence of ID (88.4%), as pain is often underrecognized among individuals with ID (McGuire et al. 2010). Abdominal pain was assessed using a single item specifying severe pain that was diagnosed by a medical professional, which likely identified a group of children with greater abdominal pain symptomatology and therefore impact. Future studies should incorporate validated instruments for the comprehensive assessment of pain (Ely et al. 2016).

Second, while well-validated measures of SIB prevalence and severity were used in this study, these measures do not provide detailed information about the function, exact topography, and clinical course of SIB. Pain-related SIB may differ in topography from SIB that are unrelated to pain (Breau et al. 2003), and specific topographies and functions of SIB have been associated with specific genetic syndromes (Huisman et al. 2018). In this sample, review of RBS-R items suggested a complex profile of multiple topographies of SIB, which may reflect multiply maintained behavior (Derby et al. 2000; Smith et al. 1993). As such, more comprehensive functional assessment of SIB among individuals with specific ASD-associated disruptive mutations is warranted for future research. Finally, additional research is needed to understand the trajectory and stability of SIB among

individuals with mutations to ASD-risk genes—for example, whether early repetitive motor behaviors or adaptive impairments predict later SIB and whether SIB persists over time. In general, our understanding of challenging behaviors and chronic pain in this population is significantly limited and represents a crucial area for future study.

**Author Contributions** E.C.K.N. conceptualized the manuscript, performed data analyses, compiled genotype data, and drafted the majority of the manuscript. S.W.T. contributed to conceptualization, provided input on analyses, and drafted sections of the manuscript. K.A. and D.C. contributed to interpretation of data analyses and drafted sections of the manuscript. A.S.W. led acquisition of phenotype data. E.E.E., R.A.B., and R.K.E. acquired genotype and phenotype data, provided conceptual input, and provided critical revisions to the manuscript. E.C.K.N., S.W.T., K.A., D.C., A.S.W., E.E.E., R.A.B., and R.K.E. reviewed and approved the final manuscript.

**Funding** This work was supported by the National Institutes of Mental Health [MH100047 to RAB; MH101221 to EEE] and the National Institute of Diabetes and Digestive and Kidney Disease [K23 DK118111 to SWT].

**Data Availability** The data that support the findings of this study are available on request from the National Database for Autism Research (RRID: SCR_004434).

## Compliance with Ethical Standards

**Conflict of interest** E.E.E. is on the Scientific Advisory Board of DNAnexus, Inc. The remaining authors have no conflicts of interest to report.

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