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Author(s)	Leader, Geraldine; Forde, Jennifer; Naughton, Katie; Maher, Leanne; Arndt, Sophia; Mannion, Arlene
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Gastrointestinal Symptoms, Sleep Problems, Challenging Behaviour, Comorbid Psychopathology and Autism Spectrum Disorder Symptoms in children and adolescents with 15q Duplication Syndrome.

Geraldine Leader

Jennifer Forde

Katie Naughton

Leanne Maher

Sophia Arndt

Arlene Mannion

National University of Ireland, Galway.

Corresponding author: Geraldine Leader, Ph.D., Irish Centre for Autism and Neurodevelopmental Research, School of Psychology, National University of Ireland, Galway, Ireland. Tel: 00353 91 493434, Fax: 00353 91 521355.

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Abstract

Background: Comorbidity is the presence of at least two disorders in one person at one time. This study examined the frequency of gastrointestinal symptoms (GI), sleep problems, comorbid psychopathology, challenging behaviour, and autism spectrum disorder (ASD) symptoms in children and adolescents with Duplication 15q syndrome (Dup15q), aged 3 – 17 years. This study also examined whether challenging behaviour in Dup15q is predicted by age, gender, presence of an intellectual disability, sleep problems, GI symptoms and comorbid psychopathology.

Method: Parental measures were completed by 101 parents of children and adolescents with Dup15q. Questionnaires comprised of the Children's Sleep Habits Questionnaire, Behaviour Problem Inventory – Short Form, GI Symptom Inventory, Social Communication Questionnaire and the Child Behavior Checklist.

Results: Sleep problems (94%), GI symptoms (87%) and challenging behaviour (100%) were common comorbidities represented in the sample in this study. Significant relationships were found between challenging behaviour and the presence of co-occurring sleep problems, GI symptoms, comorbid psychopathology, and ASD symptoms. Further analysis revealed that these comorbidities also predicted challenging behaviour.

Conclusion: This research demonstrated the importance of studying the relationships between GI symptoms, sleep problems, comorbid psychopathology, ASD symptoms, and challenging behaviour in Dup15q and how these conditions can shape the Dup15q phenotype.

Keywords: Dup15q, comorbidity, sleep problems, gastrointestinal symptoms, challenging behaviour, autism spectrum disorder.

1. Introduction

1.1 Dup15q Syndrome

Duplication 15q syndrome (Dup15q) is a neurodevelopmental disorder that is characterised by hypotonia and motor delays, intellectual disability (ID), poor speech, and epilepsy including infantile spasms and autism spectrum disorder (ASD)-like behaviour (Finucane et al. 2016; Miller et al. 2009; Xie, 2015). Developmental delay and ID affect all individuals with Dup15q, and expressive language is often poor (Battaglia, 2008). More than half of those with Dup15q have epilepsy, and seizures usually begin from as early as six months up to nine years of age (Battaglia et al. 1997).

Dup15q involves copy number gains of the maternal chromosome 15q11.2-q13 region (Shaaya et al. 2015). The extra copy or copies most commonly arise by one of two mechanisms: A maternal isodicentric duplication typically comprising two extra copies of 15q11.2-q13.1 and resulting in tetrasomy for 15q11.2-q13.1 (80% of cases); or a maternal interstitial duplication that typically includes one extra copy of 15q11.2-q13.1 within chromosome 15, resulting in trisomy for 15q11.2-q13.1 (20% of cases) (Finucane et al. 2016). One of the most common copy variations associated with ASD are duplications of the chromosome 15q11.2-q13.1 (Urraca et al. 2016).

Dup15q is diagnosed by detecting at least one extra maternally derived copy of the Prader-Willi/Angelman critical region (PWACR), which is located within chromosome 15q11.2-q13.1 and is approximately 5 Mb long (Finucane et al. 2016). The PWACR is imprinted with maternally derived increases in copy number causing Dup15q, while paternally derived increases are typically associated with different neurodevelopmental phenotypes (Urraca et al. 2013).

The prevalence of Dup15q in the general population is unknown but may be as high as 1:5000 (Kirov et al., 2014). With respect to patients referred for clinical testing due to developmental concerns or multiple anomalies, the prevalence of Dup15q is approximately 1:508 (Malhotra & Sebat, 2012). Among those with ID, the prevalence of Dup15q is 1:584 (Malhotra & Sebat, 2012).

1.2 Dup15q and Comorbidity

Comorbidity is the co-occurrence of two or more disorders in the same person (Matson & Nebel-Schwalm, 2007). Research suggests that many of the core symptoms of ASD overlap with Dup15q. Some of these symptoms include social and communication impairments, and stereotypy (Battaglia et al., 2010). Between 0.5-3% of ASD cases are associated with chromosome 15 abnormalities (Sanders et al. 2015; Weigel et al. 2012). Duplications in the 15q region are the most common chromosome duplications associated with ASD (Abrahams & Geschwind, 2008; Cook et al. 1998; Depienne et al. 2009; Moreno-De-Luca et al. 2013). The prevalence of Dup15q in ASD varies between 1:253 and 1:522 (Depienne et al. 2009; Malhotra & Sebat, 2012; Moreno-De-Luca et al. 2013).

Several studies estimate that between 0.25–3% of all ASD cases may be the result of Dup15q (Cook et al., 1997; Depienne et al., 2009; Sanders et al., 2015; Schroer et al., 1998; Sebat et al., 2007; Vorstman et al., 2006). Ageeli et al. (2014) reviewed 30 cases of individuals with Dup15q and 74% were reported to have a diagnosis of ASD. In a study by Hogart et al. (2010), 92% of individuals with Dup15q met the criteria for ASD. Similarly, a study by DiStefano et al. (2016) identified that all individuals with Dup15q met the criteria for an ASD diagnosis. In addition, previous research has reported that more cases of maternally derived Dup15q meet the criteria for ASD compared to paternally derived Dup15q (Urraca et al., 2013).

Battaglia et al. (2010) suggested that individuals with Dup15q are not "true autistic", but distinct "autistic-like" persons who show symptoms of ASD (Battaglia et al. 2010). In 13 individuals with Dup15q, shared ASD behaviours were reported including cognitive impairments, social impairments, and stereotypy behaviour (Battaglia, 2010). DiStefano et al. (2016) found that children with Dup15q who met the criteria for ASD also displayed significantly more impairments in motor and daily living skills.

Common comorbidities in ASD include gastrointestinal symptoms, sleep problems, attention-deficit/hyperactivity disorder (AD/HD), epilepsy, anxiety, toileting problems, feeding problems, emotional and behavioural problems, self-injury, aggression and tantrum behaviour (Devlin et al. 2008; Francis et al. 2017; Mannion & Leader, 2013; 2014a; 2014b; Leader & Mannion, 2016a; Leader et al., 2020; Maskey et al. 2013). Research has identified comorbidities in other rare genetic conditions such as Fragile X Syndrome (Newman et al. 2015).

1.3 Dup15q and Gastrointestinal Symptoms

Gastrointestinal (GI) symptoms have rarely been reported in the research literature for individuals with Dup15q. Previous research has found that infants with Dup15q experienced feeding difficulties within their first nine months of life (Schroer et al. 1998). Shaaya et al. (2015) examined medical records of 46 individuals with Dup15q to investigate the presence of GI symptoms and the treatments they were receiving. Findings revealed that GI symptoms were present in 76.7% of individuals with an isodicentric duplication and 87.5% with an interstitial duplication. The most common symptoms were gastroesophageal reflux, and constipation, with 30% of individuals reporting both (Shaaya et al. 2015). Their study reported that irritable and aggressive behaviour decreased in many patients when treating GI symptoms (Shaaya et al., 2015). In light of Shaaya et al. (2015) findings, GI

symptoms are common and may display atypically. However, diagnosing the presence of GI symptoms may prove difficult for individuals who are nonverbal. The majority of studies on GI symptoms in this population are based on parent report. Rates of GI symptoms may be even higher if the parent/caregiver is not aware of their child's GI symptoms. Some GI symptoms may be easier to recognise such as constipation or diarrhoea. Other symptoms, such as nausea, bloating, or abdominal pain may be more difficult for parents to observe.

1.4 Dup15q and Sleep Problems

Sleep problems may comprise of obstructive sleep apnea, abnormal arousal, abnormal circadian rhythm in rapid eye movement (REM) sleep, night awakenings, and excessive daytime sleepiness (Maas et al. 2010). Due to the low prevalence of Dup15q, minimal research has been conducted on the co-occurrence of sleep problems in Dup15q. Sleep problems are prevalent in those with ASD (Urraca et al. 2013), however, only few studies have examined sleep problems in Dup15q. Ajayi et al. (2017) reviewed data from 96 individuals with Dup15q and found evidence of sleep disturbances within the sample. The incidence of sleep problems were not given in the study, but the types of sleep disturbances found were where individuals awaken in the middle of the night. Most individuals fell back to sleep in under 25 minutes, while a small remained awake for more than one hour. Similarly, Urraca et al. (2013) examined 14 children with Dup15q and found that all children presented with sleep problems. However, those with a paternal duplication of 15q reported more sleep problems than those with a maternal duplication, such as higher frequencies of bedtime resistance, sleep onset delay, sleep anxiety, night wakings, parasomnias, sleep disordered breathing, daytime sleepiness, and had a reduced sleep duration.

1.5 Dup15q and Challenging Behaviour

Challenging behaviour such as aggression, stereotypies, ritualistic behaviour, hyperactivity, short attention span, and impulsive behaviour have frequently been associated with Dup15q (Kalsner & Chamberlain, 2015; Wisniewski et al. 1979; Schinzel. 1981; 1990; Van Bon et al. 2009).

1.6 Dup15q and Comorbid Psychopathology

Comorbid psychopathology refers to the occurrence of two or more forms of psychopathology within an individual (Matson & Nebel-Schwalm, 2007). These disorders may range from mood disorders, anxiety disorders, Attention-Deficit/ Hyperactivity Disorder (AD/HD) and various other psychological disorders (Mannion et al. 2014). Comorbid psychopathology frequently seen in Dup15q, including hyperactivity, anxiety, or emotional lability (Battaglia et al., 1997).

1.7 Gaps in Current Knowledge

The overlap between Dup15q and ASD may suggest some of the same comorbid conditions may be present. However, research investigating comorbidities in Dup15q is currently limited. Further research is needed on GI symptoms in Dup15q as increased awareness is critical for early diagnosis and treatment. Research investigating the prevalence of challenging behaviour in this sample is currently under researched, therefore more research is required in order to fully define the behavioural profile of Dup15q. Comorbid psychopathology with ASD is an area that has been prominently researched (Matson & Nebel-Schwalm, 2007; Leyfer et al. 2006), however very little research has been conducted in Dup15q. Due to the overlap in ASD and Dup15q symptoms, this emphasises the importance of researching comorbid psychopathology in Dup15q.

1.8 Current Study

Research has identified GI symptoms, sleep problems and comorbid psychopathology as predictors of challenging behaviour in ASD (Adams et al. 2014; Leader & Mannion, 2016b; Mazurek, & Sohl, 2016; Stratis & Lecavalier, 2013; Yang et al. 2018). This study aimed to investigate the frequency of GI symptoms, sleep problems, challenging behaviour, comorbid psychopathology and ASD symptoms in children and adolescents with Dup15q. This study examined the relationship between these comorbidities in Dup15q, as well as the predictors of challenging behaviour.

2. Method

2.1 Sample

This study included 101 children and adolescents with a diagnosis of one of the following: 15q11.1-q13.1, (45.5%; *n*=46), 15q13.2 q13.3, (41.6%; *n*=42) or 15q 13.3 (3%; *n*=3) or 15q 11.2 (9.9%; *n*=10). The mean age of the sample was 7.9 years (*S.D* = 3.76), ranging from 2 to 18 years. Fifty-seven percent (*n* = 58) were males and 43% (*n* =43) were female. Caregiver information on professional diagnosis was obtained. It was reported that 46.5% (*n*=47) received their diagnosis from a geneticist, 41.6% (*n*=42) from a paediatrician, 7.9% (*n*=8), from a neurologist, 3% (*n*=3), from a child psychiatrist and 1% (*n*=1) from a psychologist. It was reported that 80.2% (*n*=81) had an intellectual disability (ID) with 17.2% (*n*=17) having a mild ID, 35.4% (*n*=35) having a moderate ID and 28.3% (*n*=28) having a severe ID. Children and adolescents with Dup15q were from the following countries: United States of America (USA; 38.6%, *n*=39), United Kingdom (UK; 20.8%, *n*=21), Australia, 7.9% (*n*=8), Germany, 5.9% (*n*=6), Ireland, 5% (*n*=5), Canada, 5% (*n*=5), France, 5% (*n*=5) Italy, 3% (*n*=3) Brazil, 3% (*n*=3) and Singapore, 2% (*n*=2). Other countries included Austria, New Zealand, Norway, and New Caledonia.

2.2 Informants and Procedure

Informants were parents of children and adolescents with a diagnosis of Dup15q. Parents were recruited through social media, Dup15q worldwide organisations, and online parent support groups. If parents wished to participate in the study, they were provided with a participant information form and a consent form to complete. Parents provided consent for their children as they were completing questionnaires on their behalf. Assent for minors was not obtained. Once consent was obtained, the informants were provided with the battery of the below questionnaires to complete in their own time. Rating scales were completed by parents independently according to the instructions which were printed on the top of each questionnaire.

2.3 Ethical Approval

This study received full ethical approval from the School of Psychology Research Ethics Committee at National University of Ireland, Galway (NUI Galway). Parental consent was obtained from all parents of children and adolescents with Dup15q involved in this research and confidentiality was maintained.

2.4 Measures

2.4.1 Demographic Information. A self-constructed questionnaire provided information on the child or adolescent with Dup15q's age, gender, whether they had an independent diagnosis of Dup15q, specific type of duplication, and what age they were diagnosed. It examined whether they had epilepsy at present, had a seizure before diagnosis of Dup15q or whether they presented with GI symptoms occurring prior to the diagnosis of Dup15q. It also included questions on whether children or adolescents with Dup15q presented with an ID, what level of ID they were diagnosed with if any, any experience of migraines, if they received educational intervention and if so, how many hours per week.

Lastly, it included if the child is taking medication and if so, what condition it was used to treat and whether they were diagnosed with any additional co-occurring disorders.

2.4.2 Behavior Problems Inventory – Short Form. The Behavior Problems Inventory (BPI-S; Rojahn et al. 2012) is a shortened version of the BPI-01, an instrument that assesses the frequency and severity of challenging behaviour. It consists of a 30-item questionnaire and is made up of three behaviour subscales: Self-Injurious Behavior (SIB; 8items), Aggressive/Destructive Behavior (10 items), and Stereotyped Behavior (12 items). The BPI-S is scored on a 5-point frequency scale (never = 0, monthly = 1, weekly = 2, daily = 3, hourly = 4) and a 4-point severity scale (no problem = 0, a slight problem = 1, a moderate problem = 2, a severe problem = 3). Rojahn et al. (2012) established good internal consistency reliability and the data showed that the BPI-S performed as well as, if not better than the BPI-01 in terms of the item correlations.

2.4.3 Gastrointestinal Symptom Inventory. The GI Symptom Inventory (GSI; Autism Treatment Network, 2005) consists of 35-items assessing GI symptoms. The questionnaire is scored dichotomously dependent on the presence or absence of symptoms. It assesses specific symptomatology including abdominal pain, nausea, bloating, constipation, and diarrhoea, nausea, and other stomach symptoms. While the measure has not been validated, it has been used in published studies (Leader et al. 2018; Mannion & Leader, 2016; Mazurek et al. 2013; Mazefsky et al. 2010). The GSI is based on previous questionnaires and on clinical symptom assessment for children with ASD and identified GI disorders.

2.4.4 Children's Sleep Habit's Questionnaire. The Children's Sleep Habits Questionnaire (CSHQ) (Owens et al. 2000) consists of a 52- item parental-report, used to screen for sleep problems. It is divided into eight different subscales: bedtime resistance,

sleep-onset delay, sleep duration, sleep anxiety, night waking, parasomnias, sleep disordered breathing, and daytime sleepiness (Owens et al. 2000). Parents were asked to recall sleep behaviour occurrences within the last week. Forty-two items are rated on a three-point Likert-scale, with responses ranging from 'Usually' (5 or more times a week), 'Sometimes' (2–4 times a week), and 'Rarely' (never or one time a week). Thirty-three of the items are computed for a total sleep disturbance score and for the subscales within the questionnaire. The CSHQ has demonstrated good internal consistency, ranging from .68 to .78, and good test-retest reliability between .62 and .79 (Shahid et al. 2012).

2.4.5 Social Communication Questionnaire. The Social Communication Questionnaire (SCQ; Rutter et al. 2003) is a brief, 40-item, parent-report screening measure that focuses on items relating to ASD symptomatology (social interaction, communication, and repetitive/stereotypic behaviour). Each item in the SCQ requires a dichotomous "yes"/ "no" response, and each scored item receives a value of 1 point for abnormal behaviour and 0 points for the absence of abnormal behaviour/normal behaviour. Marvin et al. (2017) found that the full SCQ had high internal consistency (with Cronbach's alpha of .94 for verbal children and .89 for nonverbal children, where all children has a diagnosis of ASD).

2.4.6 Child Behavior Checklist. The Child Behavior Checklist (CBCL), (Achenbach & Rescorla, 2001), is a 118-item parent report form measuring emotional, behavioural, and social problems in children and adolescents. The CBCL assesses internalizing (i.e., anxious, depressive, and overcontrolled) and externalizing (i.e., aggressive, hyperactive, noncompliant, and under controlled) behaviours based on the following subscales; anxiety and depression, social withdrawn, somatic complaints, social problems, thought problems, attention problems, rule-breaking behaviour, and aggressive behaviour. The CBCL also has a scale set showing which scores are associated with disorders from the Diagnostic and Statistical Manual of Mental Disorders (DSM-5;

American Psychiatric Association, 2013) such as anxiety, oppositional defiant disorder, conduct problems, somatic problems, affective problems, and attention deficit disorder. It has demonstrated a high rate of reliability between the scales of the CBCL and actual psychological diagnosis (Mazefsky et al., 2010). Cronbach's alpha values ranged from .46 to .93 on the various subscales (Mazefsky et al., 2010).

3. Results

3.1 Analyses and Rationale

The SPSS Statistical Program, Version 23 was used to conduct statistical analyses. A correlation analysis using Pearson correlations was conducted between challenging behaviour (subscales of BPI-S, SIB frequency and severity, aggressive/destructive behavior frequency and severity and stereotyped behavior frequency), and total GI symptoms (total score of GSI), total sleep problems (total score of CSHQ), comorbid psychopathology (total score of CBCL) and total ASD symptoms (total score of SCQ). The rationale for the Pearson correlations was to investigate whether there was a relationship between challenging behaviour and comorbid conditions (challenging behaviour, GI symptoms, sleep problems, comorbid psychopathology, and ASD). A multiple linear regression analysis was conducted to investigate if age, gender, diagnosis of ID, GI symptoms, sleep problems and comorbid psychopathology predicted challenging behaviour in children and adolescents with Dup15q. The rationale for the multiple linear regression was to investigate the predictors of challenging behaviour, including demographic information (age, gender, ID), and comorbid conditions (GI symptoms, seep problems, and comorbid psychopathology).

3.2 Current Comorbid Diagnosis

The frequency of a comorbid diagnosis was 80.2% (*n*=81) in the sample, a comorbid diagnosis was reported if the individual had an additional diagnosis of at least one of the

following: an ID, ASD, AD/HD, an anxiety disorder, migraines or epilepsy. A total of 63.4% (*n* = 64) of the sample were receiving medication, such as melatonin (22.8%, *n* = 23), Keppra (6.9%, *n* = 7), Tegretol (2%, *n* = 2), and Movical (4%, *n* = 4). Among the interventions used in this sample, applied behaviour analysis was the most frequent at 28.7% (*n* = 29), followed by special education needs at 17.8% (*n* = 18). Occupational therapy and education, health and care plans were the least reported intervention used at 5% (*n* = 5) respectively. A summary of the remaining comorbid diagnoses, medications and interventions used are given in Table 1.

3.3 GI symptoms occurring prior to the diagnosis of Dup15q syndrome

GI symptoms occurring prior to the diagnosis of Dup15q were investigated using a question from the Demographic Information questionnaire. GI symptoms occurring prior to the diagnosis of Dup15q were prevalent across children and adolescents within this study. As can be seen in Table 2, the prevalence of GI symptoms occurring prior to the diagnosis of Dup15q was reported in 49.5% (*n* = 50) of the sample. Constipation was the highest reported GI symptom occurring prior to the diagnosis of Dup15q where it was reported in 44.6% (*n* = 45) of children and adolescents with Dup15q, followed by abdominal pain reported in 27.7% (*n* = 28). Nausea was the least frequent symptom reported in 12.9% (*n* = 13). The remaining frequencies and percentages of GI symptoms occurring prior to the diagnosis of Dup15q can be seen in Table 2.

3.4 Comorbidities in Dup15q syndrome

This study found a high prevalence of GI symptoms, sleep problems, challenging behaviour, comorbid psychopathology, and ASD symptoms and in those with Dup15q. GI symptoms were attained from the GSI, sleep problems from the CSHQ, challenging

behaviour from the BPI-S, ASD symptoms from the SCQ, and comorbid psychopathology from the CBCL. It was found that 87% (n = 87) of children and adolescents with Dup15q presented with at least one GI symptom, 21.8% (n = 22) presented with two symptoms, while 23.8% (n = 24) had three symptoms, 20.8% (n = 21) and 11.9% (n = 12) presented with four and five GI symptoms respectively within the last three months.

The mean scores and standard deviations for the BPI-S were calculated for the five subscales (see Table 4). Stereotyped behaviour was the most commonly reported behaviour problem in Dup15q (M = 17.45, SD = 12.96), followed by aggressive/destructive behaviour severity (M = 8.1, SD = 7.39). SIB severity was the least reported behaviour problem within the sample (M = 3.14, SD = 2.7). One hundred percent (n = 101) of the sample exhibited at least one form of challenging behaviour, 87% (n = 88) displayed two forms, and 75% (n = 76) displayed all three topographies of behaviour. ASD symptoms were present in 64.4% (n = 65) of the sample. The prevalence of sleep problems in this sample was 94.1% (n = 95). The means and standard deviations were calculated for challenging behaviours and the mean score for the CBCL was 66.42 (SD = 8.86) (See Table 3 and 4).

3.5 Correlational Analysis

Significant correlations were found between challenging behaviour (based on the five subscales of the BPI-S) and GI symptoms, sleep problems, comorbid psychopathology, and ASD symptoms. In relation to SIB severity, significant positive correlations were found between this behaviour problem and GI symptoms (r (101) = .29, p < .001), sleep problems (r (101) = .32, p < .001), and comorbid psychopathology (r (101) = .26, p < .05). Likewise, significant correlations were found between SIB frequency and the following total scores: GI symptoms (r (101) = .32, p < .001), sleep problems (r (101) = .32, p < .001), and comorbid psychopathology (r (101) = .28, p < .001). Small to moderate positive correlations were

found between aggressive/destructive behavior severity and the following: GI symptoms (r (101) = .20, $p < .05$), sleep problems (r (101) = .31, $p < .001$), comorbid psychopathology (r (101) = .35, $p < .001$), and presence of ASD symptoms (r (101) = .34, $p < .001$). Similar relationships were found between aggressive/destructive behavior frequency and GI symptoms (r (101) = .20, $p < .05$), sleep problems (r (101) = .30, $p < .001$), comorbid psychopathology (r (101) = .38, $p < .001$), and presence of ASD symptoms (r (101) = .38, $p < .001$). Lastly, significant positive correlations were found between stereotyped behavior frequency and the presence of ASD symptoms. Table 5 gives a summary of the findings.

3.6 Multiple Regression

A hierarchical multiple linear regression was conducted to examine if age, gender, diagnosis of ID, sleep problems, GI symptoms and comorbid psychopathology predicted frequency and severity of challenging behaviour (SIB, aggressive/destructive behavior, stereotyped behaviour). Age of children or adolescents with Dup15q, gender, and presence of ID were entered in the first step of the model as possible predictors of SIB frequency, which is a subscale of the BPI-S. These predictor variables were followed by the addition of total score on the CSHQ in the second step. The total score on the GSI was added in the third step of the model. Finally, the total for the CBCL were entered in the fourth step of the model. These same steps were followed for frequency and severity of all five subscales of the BPI-S (i.e. SIB frequency, SIB severity, aggressive/destructive behavior frequency, aggressive/destructive behavior severity, and stereotyped behavior frequency). For stereotyped behavior in the BPI-S, there is no severity subscale.

In relation to predictors of SIB frequency, it was found that total score on the CSHQ predicted SIB frequency, $F_{(4, 96)} = 4.88$, $p < .05$. Total score on the GSI predicted SIB frequency, $F_{(5, 95)} = 4.47$, $p < .05$. Total CBCL predicted SIB frequency, $F_{(6, 94)} = 3.73$, $p <$

.05. A summary of regression analysis for variables predicting SIB frequency are given in Table 6.

---Insert Table 6 here---

In relation to SIB severity, total score on the CSHQ emerged as a significant predictor of SIB severity, $F_{(4,96)} = 4.81$, $p <. 05$. Total score on the GSI was a significant predictor, $F_{(5,95)} = 5.07$, $p <. 05$. Total CBCL was significant, $F_{(6,94)} = 6.03$, $p <$ .05. A summary of regression analysis for variables predicting SIB severity are presented in Table 7.

---Insert Table 7 here---

With regards to the regression for predictors of aggressive/destructive behavior frequency, CSHQ total scores were a significant predictor of aggressive/destructive behavior frequency, $F_{(4,96)} = 3.17$, $p <. 05$. Total GSI score was a significant predictor, $F_{(5,95)} = 2.69$, $p < .05$. CBCL total scores were a significant predictor of aggressive/destructive behavior frequency, $F_{(6,94)} = 3.40$, $p <.05$. A summary of regression analysis for variables predicting aggressive/destructive behavior frequency are presented in Table 8.

---Insert Table 8 here---

In the regression conducted for predictors of aggressive/destructive behavior severity, CSHQ total scores were a significant predictor, $F_{(4,96)} = 2.86$, $p < .05$. GSI total scores were also significant, $F_{(5,95)} = 2.42$, $p <.05$. CBCL total scores were a significant predictor, $F_{(6,94)} = 3.80$, $p <.05$. A summary of regression analysis for variables predicting aggressive/destructive behavior severity are presented in Table 9.

---Insert Table 9 here---

In the regression conducted to examine the predictors of stereotyped behavior frequency, CSHQ total scores were a significant predictor, $F_{(4,96)} = 5.26$, $p < .05$. GSI total scores were a significant predictor, $F_{(5,95)} = 4.27$, $p < .05$. CBCL total scores were a significant predictor of stereotyped behavior frequency, $F_{(6,94)} = 3.52$, $p < .05$. A summary of regression analysis for variables predicting stereotyped behavior frequency are presented in Table 10.

---Insert Table 10 here---

4. Discussion

The current study examined the relationship between challenging behaviour, and GI symptoms, sleep problems, comorbid psychopathology and ASD symptoms in children and adolescents with Dup15q. This study examined the predictors of challenging behaviour. High rates of comorbidities, including GI symptoms, sleep problems and challenging behaviour were found in this sample.

Within this sample, 80.2% of children and adolescents with Dup15q had a comorbid diagnosis. A comorbid diagnosis included ID, ASD, AD/HD, an anxiety disorder, migraines, or epilepsy. This finding is similar to previous research by Battaglia (2008) who reported that developmental delay and ID affect all individuals with Dup15q. It was found that 27% of individuals with Dup15q had a diagnosis of epilepsy. This finding is supported to those of DiStefano et al. (2016) who found that 31% of their participants with Dup15q had active epilepsy.

High rates of challenging behaviour were reported in this study with all children and adolescents with Dup15q engaging in at least one form of challenging behaviour and 75% engaging in all three topographies of challenging behaviour. This finding is the highest reported prevalence of challenging behaviour in Dup15q research. Symptoms of ASD were

found in 62% of children and adolescents with Dup15q. This finding was supported by Urraca et al. (2016).

High levels of ASD symptoms reported in this sample may be suggestive of the high frequency of challenging behaviour as previous research indicates that challenging behaviour occurs in over 94% of individuals with ASD (Matson et al. 2008). This finding highlights the overlap between symptoms of ASD and Dup15q. Significant relationships were found between ASD symptoms and the frequency and severity of aggressive behaviour. The high comorbidity of ASD symptoms represented in the sample confirm the overlapping phenotype of Dup15q and ASD. Previous research has identified that comorbidities such as sleep problems, GI symptoms, comorbid psychopathology and challenging behaviour are highly prevalent in ASD. Results from this study may indicate that the high frequencies of these comorbidities in the sample may be representative of the fact that ASD commonly co-occurs with Dup15q. Going forward, duplications of chromosome 15 should be considered in all cases of ASD.

Overall, 87% of children and adolescents with Dup15q reported that they experienced at least one GI symptom within the past 3 months. These findings are supported by Shaaya et al. (2015) who found that GI symptoms were present in 76.7% of individuals with an isodicentric duplication and 87.5% with an interstitial duplication. Constipation was the most common reported GI symptom (55%) which is similar to Shaaya et al. (2015), who reported that 60% of individuals with Dup15q commonly experienced constipation. The current study found that 49% of children and adolescents with Dup15q experienced GI symptoms occurring prior to the diagnosis of Dup15q. Therefore, GI symptoms are present from a young age. Significant correlations were found between total GI symptoms and the severity and frequency of SIB. Further analysis revealed that GI symptoms predicted

challenging behaviour; specifically the severity and frequency of SIB, the severity and frequency of aggressive behaviour and the frequency of stereotypy behaviour.

Sleep problems were identified as the most common comorbid condition in Dup15q with 94% of children and adolescents with Dup15q being affected. This is similar to Urraca et al. (2016), who found that all 15 individuals with Dup15q presented with sleep problems. In addition, this study found strong associations between sleep problems and challenging behaviour. When further analysis was carried out results showed that sleep problems predicted challenging behaviour on all the subscales of challenging behaviour (frequency and severity of SIB, frequency and severity of aggressive/destructive behavior and frequency of stereotyped behaviour). This novel finding suggests that sleep problems should be considered when challenging behaviours are presented in children and adolescents with Dup15q.

Comorbid psychopathology was found to co-occur with Dup15q. Results from the current study study revealed an association between comorbid psychopathology and challenging behaviour in Dup15q. Comorbid psychopathology predicted SIB, aggressive/destructive behavior, and stereotyped behavior, as well as somatic problems and sleep problems.

Many of the co-occurring conditions measured in this study are associated with hyperarousal. Previous research has identified that the hyperarousal is associated with elevated levels of cortisol in insomnia patients (Rodenbeck *et al. 2002;* Vgontzas et al. 2001). Similar findings have been reported in the ASD population, whereby individuals with ASD experiencing sleep problem such as insomnia report elevated rates of cortisol compared to controls (Richdale & Prior, 1992; Corbett *et al*. 2008; Baker *et al.* 2019). This elevation in cortisol provides support for a hyperarousal hypothesis of insomnia for individuals with

ASD. Regarding GI symptoms, Ferguson et al. (2017) identified a relationship between the automatic nervous system and GI problems whereby a significant relationship was identified between parasympathetic psychophysical markers and lower GI tract symptoms, moderated by anxiety in the ASD population. Findings from a review conducted by Patriquin *et al.* (2019) support the relationship between hyperarousal and emotional and behavioural problems in individuals with ASD. Research by Tordjman et al. (2014) identified that high cortisol levels reported in children with ASD, with higher cortisol levels associated with more severe symptoms of ASD. Given that the autonomic nervous system is altered in many with ASD, which is a co-occurring condition with Dup15q, it may be possible that this may also be a potential mechanism for the findings reported in this study. It may be the case that some shared mechanisms among these comorbid conditions can lead us towards treatment targets in the future.

The current study is a representative sample of children and adolescents with Dup15q as recruitment was conducted worldwide. Children and adolescents with Dup15q did not need to present with any comorbid condition in order to take part in their research. It is possible that parents may have been more interested in taking part in the research if their child presented with comorbid conditions, which can be considered a limitation of the study. During recruitment, it was specifically stated that children and adolescents did not need to experience comorbid conditions in order to take part in the study.

This present study is the first to investigate challenging behaviour, GI symptoms, sleep problems, comorbid psychopathology and ASD symptoms within a sample of children and adolescents with Dup15q. There were some limitations. This study relied on parent – report. This may be a limitation for comorbidities such as GI symptoms, when measuring symptoms such as abdominal pain and nausea. However, Gorrindo et al. (2012) report GI symptoms in children with ASD, evaluated by paediatric gastroenterologists and compared

with parental report of GI symptoms. Parental report of presence of any GI symptoms in ASD was recorded as concurrent with a physician's diagnosis of GI symptoms, validating parental report for reporting GI symptoms in children.

The current study has important implications for clinical practice. Firstly, these findings support current best practice assessments in Dup15q, which should include routine assessments of sleep disturbances and health problems. The results suggest the importance for clinicians to be aware of the frequency of sleep problems, GI symptoms and comorbid psychopathology for those with Dup15q and how these factors may be predictors to challenging behaviour. Previous literature has shown how prevalent these factors are in this population, and with the results of this study more information has been provided on the association between these factors and challenging behaviour. This awareness is beneficial to clinicians to better understand the relationship between challenging behaviour and sleep problems, GI symptoms or comorbid psychopathology for children and adolescents with Dup15q.

Future research is needed to determine if these comorbidities of challenging behaviour, sleep problems, GI symptoms, comorbid psychopathology and ASD symptoms are common in adults with Dup15q. Future research may seek to further investigate predictors of challenging behaviour with adults with Dup15q by examining the predictors found from this study. Longitudinal research is also needed to determine if these comorbidities increase or decrease as children and adolescents with Dup15q become adults.

The maternally derived duplications have a range of dysmorphic features such as ASD. However, paternally derived duplications range from normal phenotype to significant anomalies. The high incidence of ASD in this study suggest that the sample were primarily maternally derived cases. Future research is needed for paternally derived cases of Dup15q

in order to further investigate common comorbidities associated with this population, and how they shape the phenotype of paternally derived Dup15q.

In conclusion, this study was the first study to demonstrate that children and adolescents with Dup15q show a wide range of comorbid issues such GI symptoms, sleep problems, comorbid psychopathology, ASD symptoms and challenging behaviour. This study has also revealed that GI symptoms, sleep problems, comorbid psychopathology, and ASD symptoms are correlated with challenging behaviour. Furthermore, analysis of the individual factors found that GI symptoms such as nausea and constipation, sleep problems and comorbid psychopathology predict challenging behaviour. These findings of GI symptoms, sleep problems and comorbid psychopathology predicting challenging behaviour provide avenues for future research to investigate suitable treatments for challenging behaviour. These findings suggest targets for investigation and intervention to reduce behavioural issues. For example, due to the variables of GI symptoms predicting challenging behaviour, treatment of these GI symptoms may then have an impact on the reduction of challenging behaviour. Similarly, treatment of sleep problems may also impact challenging behaviour. These possible targets for investigation and intervention are an area of future research that needs to be further explored. Overall, these findings will provide researchers and clinicians with a better understanding of comorbidities and predictors of challenging behaviour for individuals with Dup15q.

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Table 1.

Comorbid disorder diagnoses, medication use and current intervention received.

Characteristic	Frequency	Percentage
Frequency of a comorbid disorder	81	80.2
ID	94	93.1
ASD	33	32.7
AD/HD	16	15.8
Migraines	10	9.9
Epilepsy	26	25.7
Anxiety Disorder	16	15.8
General Anxiety Disorder	5	5
Social Anxiety Disorder	4	4
Separation Anxiety Disorder	4	4
Medication		
Children receiving medication	64	63.4
Melatonin	23	22.8
Levetiracetam	7	6.9
Carbamazepine	2	2
Marcogol	4	4
Intervention		
Applied Behaviour Analysis	29	28.7
Special Education Needs	18	17.8
Eclectic Treatment	13	12.9
Speech and Language	9	8.9
Mainstream School	6	5.9
Occupational Therapy	5	5
Education, Health and Care Plan	5	5
No Intervention	10	9.9

Table 2.

GI symptoms occurring prior to the diagnosis of Dup15q.

GI Symptoms	Frequency	Percentage (%)
GI symptoms occurring prior to the diagnosis of Dup15q	50	49.5
Constipation	45	44.6
Abdominal Pain	28	27.7
Diarrhoea	20	19.8
Bloating	19	18.8
Nausea	13	12.9

Table 3.

Frequencies and percentages of comorbid conditions (GI symptoms, challenging behaviour, ASD symptoms, Sleep Problems, and Comorbid Psychopathology) in Dup15q.

	Frequency	Percentage
GI Symptoms		
At least one symptom	87	87%
Two symptoms	22	21.8%
Three symptoms	24	23.8%
Four symptoms	21	20.8%
All five symptoms	12	11.9%
Challenging Behaviour		
One form	101	100%
Two forms	88	87%
Three forms	76	75%
ASD Symptoms [1]	65	64.4%
Sleep Problems [2]	95	94.1%
Comorbid Psychopathology [3]	(*M*=66.43, *SD*=8.86)	

1. Scored above 15 on the SCQ
2. Scored above 41 on the CSHQ
3. Measured using CBCL total scores

Table 4.

Means and standard deviations for subscales of challenging behaviour as measured by the BPI-S.

Subscale	*M*	*SD*
Self-injurious behavior frequency	4.72	4.19
Self-injurious behavior severity	3.14	2.7
Aggressive/destructive behavior severity	8.1	7.39
Aggressive/destructive behavior frequency	5.67	5.79
Stereotyped behavior frequency	17.45	12.96

Note: BPI-S=Behavior Problems Inventory-Short Form

Table 5.

Pearson's correlations between challenging behaviour (BPI-S subscale scores) and GI symptoms (GSI total scores), sleep problems (CSHQ total scores), comorbid psychopathology (CBCL total scores) and ASD symptoms (SCQ total scores).

	SIB Severity	SIB Frequency	Aggressive/destructive Behavior Severity	Aggressive/destructive Behavior Frequency	Stereotyped Behavior Frequency
Total GSI	.29**	.32**	.20*	.20*	0.1
Total CSHQ	.32**	.32**	.31**	.30**	.34**
Total CBCL	.26*	.28**	.35**	.38**	0.14
Total SCQ	0.09	0.12	.34**	.38**	.-.01

Note: BPI-S=Behavior Problems Inventory-Short Form, GSI=Gastrointestinal Symptom Inventory, CSHQ=Children's Sleep Habits Questionnaire, CBCL=Child Behavior Checklist; SCQ=Social Communication Questionnaire

* $p<.05$

** $p<.01$

Table 6.

Summary of regression analysis for variables predicting SIB frequency.

Variable	*B*	*B SE*	*β*	R^2
Block 1				
Age	-0.021	0.009	-0.231	0.043
Gender	-0.17	0.835	-0.02	
ID	1.27	1.03	0.122	
Block 2				
Age	-0.021	0.009	-0.224	0.134
Gender	-0.081	0.8	-0.01	
ID	1.16	0.98	0.11	
Total CSHQ	0.112	0.033	.312*	
Block 3				
Age	-0.021	0.009	-.231*	0.148
Gender	0.089	0.8	0.011	
ID	1.01	0.98	0.096	
Total CSHQ	0.091	0.036	.25*	
Total GSI	0.44	0.28	0.16	
Block 4				
Age	-0.021	0.009	-.225*	0.141
Gender	0.093	0.78	0.011	
ID	1.01	0.98	0.097	
Total CSHQ	0.087	0.037	.243*	
Total GSI	0.412	0.28	0.15	
Total CBCL	0.022	0.048	0.045	

* $p<.05$

Note: BPI-S=Behavior Problems Inventory-Short Form, GSI=Gastrointestinal Symptom Inventory, CSHQ=Children's Sleep Habits Questionnaire, CBCL=Child Behavior Checklist; SCQ=Social Communication Questionnaire

Table 7.

Summary of regression analysis for variables predicting SIB severity.

Variable	*B*	*B SE*	*β*	R^2
Block 1				
Age	0.012	0.006	-0.199	0.07
Gender	-.0.21	0.538	-0.004	
ID	1.12	0.67	0.167	
Block 2				
Age	-0.011	0.006	-0.192	0.167
Gender	-0.036	0.512	-0.007	
ID	1.05	0.63	0.155	
Total CSHQ	0.072	0.022	.311*	
Block 3				
Age	-0.012	0.005	-.202*	0.211
Gender	0.191	0.51	0.035	
ID	0.91	0.62	0.13	
Total CSHQ	0.053	0.023	.230*	
Total GSI	0.403	0.176	.228*	
Block 4				
Age	-0.011	0.006	-.186*	0.224
Gender	0.199	0.504	0.037	
ID	0.92	0.62	0.137	
Total CSHQ	0.046	0.023	.199*	
Total GSI	0.352	0.18	.199*	
Total CBCL	0.038	0.03	0.126	

* $p<.05$

Note: BPI-S=Behavior Problems Inventory-Short Form, GSI=Gastrointestinal Symptom Inventory, CSHQ=Children's Sleep Habits Questionnaire, CBCL=Child Behavior Checklist; SCQ=Social Communication Questionnaire

Table 8.

Summary of regression analysis for variables predicting aggressive/destructive behavior frequency.

Variable	*B*	*B SE*	*β*	R^2
Block 1				
Age	-0.019	0.016	-0.115	-0.004
Gender	-0.445	1.5	-0.03	
ID	1.79	1.86	0.097	
Block 2				
Age	-0.018	0.016	-0.108	0.08
Gender	-0.294	1.44	-0.02	
ID	1.59	1.78	0.086	
Total CSHQ	0.19	0.061	.302*	
Block 3				
Age	-0.018	0.016	-0.112	0.078
Gender	-0.122	1.45	-0.008	
ID	1.44	1.8	0.078	
Total CSHQ	0.17	0.065	.269*	
Total GSI	0.445	0.506	0.092	
Block 4				
Age	-0.013	0.015	-0.079	0.126
Gender	0.08	1.41	-0.005	
ID	1.5	1.74	0.082	
Total CSHQ	0.131	0.065	.207*	
Total GSI	0.163	0.505	0.034	
Total CBCL	0.212	0.085	.256*	

* $p<.05$

Note: BPI-S=Behavior Problems Inventory-Short Form, GSI=Gastrointestinal Symptom Inventory, CSHQ=Children's Sleep Habits Questionnaire, CBCL=Child Behavior Checklist; SCQ=Social Communication Questionnaire

Table 9.

Summary of regression analysis for variables predicting aggressive/destructive behavior severity.

Variable	*B*	*B SE*	*β*	R^2
Block 1				
Age	0.001	0.013	0.005	0.018
Gender	-0.774	1.18	-0.066	
ID	1.6	1.47	0.11	
Block 2				
Age	0.002	-0.012	0.012	0.107
Gender	-0.656	1.14	-0.056	
ID	1.44	1.41	0.1	
Total CSHQ	0.147	0.048	.298*	
Block 3				
Age	0.001	0.012	0.008	0.113
Gender	-0.527	1.15	-0.045	
ID	1.33	1.41	0.092	
Total CSHQ	0.132	0.051	.266*	
Total GSI	0.336	0.4	0.089	
Block 4				
Age	0.006	0.012	-0.05	0.195
Gender	-0.486	1.1	-0.042	
ID	1.39	1.36	0.096	
Total CSHQ	0.094	0.051	.190*	
Total GSI	0.065	0.393	0.017	
Total CBCL	0.205	0.066	.314*	

Note: BPI-S=Behavior Problems Inventory-Short Form, GSI=Gastrointestinal Symptom Inventory, CSHQ=Children's Sleep Habits Questionnaire, CBCL=Child Behavior Checklist; SCQ=Social Communication Questionnaire

* $p<.05$

Table 10.

Summary of regression analysis for variables predicting stereotyped behavior frequency.

Variable	*B*	*B SE*	*β*	R^2
Block 1				
Age	-0.015	0.028	0.53	0.076
Gender	-2.33	2.57	-0.089	
ID	7.79	3.18	0.241	
Block 2				
Age	-0.013	0.027	-0.046	0.132
Gender	-2.04	2.44	-0.078	
ID	7.41	3.02	.229*	
Total CSHQ	0.36	0.103	.323*	
Block 3				
Age	-0.012	0.027	-0.043	0.14
Gender	-2.25	2.47	-0.086	
ID	7.6	3.04	.235*	
Total CSHQ	0.384	0.111	.346*	
Total GSI	-0.555	0.86	-0.065	
Block 4				
Age	-0.011	0.027	-0.039	0.18
Gender	-2.25	2.48	-0.086	
ID	7.61	3.06	.235*	
Total CSHQ	0.376	0.114	.339*	
Total GSI	-0.613	0.885	-0.072	
Total CBCL	0.044	0.149	0.03	

Note: BPI-S=Behavior Problems Inventory-Short Form, GSI=Gastrointestinal Symptom Inventory, CSHQ=Children's Sleep Habits Questionnaire, CBCL=Child Behavior Checklist; SCQ=Social Communication Questionnaire

* $p<.05$