Copy Number Variation at the 22q11.2 Locus Influences Prevalence, Severity, and Psychiatric Impact of Sleep Disturbance

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Research

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Abstract

Background

Sleep disturbance is common, impairing, and may affect symptomatology in developmental neuropsychiatric disorders. Here, we take a genetics-first approach to study the complex role of sleep in psychopathology. Specifically, we examine severity of sleep disturbance in individuals with a reciprocal copy number variant (CNV) at the 22q11.2 locus and determine sleep's effect on psychiatric symptoms. CNVs (deletion or duplication) at this locus confer some of the greatest known risks of neuropsychiatric disorders; recent studies suggest the 22q11.2 deletion negatively impacts sleep, but sleep disruption associated with 22q11.2 duplication has not been investigated.

Methods

We compared subjective sleep disturbance and its relationship to psychiatric symptoms cross-sectionally and longitudinally over one year in 107 22q11.2 deletion (22qDel) carriers (14.56±8.0 years; 50% male), 42 22q11.2 duplication (22qDup) carriers (16.26±13.1 years; 54.8% male) and 88 demographically-matched controls (14.65±7.4 years; 47.1% male). Linear mixed models were used to compare sleep disturbance, assessed via the Structured Interview for Psychosis-Risk Syndromes (SIPS), across groups. Next, CNV carriers were categorized as good or poor sleepers to investigate sleep effects on multiple neurobehavioral traits: psychosis-risk symptoms (SIPS), autism-related behaviors (Repetitive Behavior Scale; RBS and Social Responsiveness Scale; SRS), real-world executive function, (Behavior Rating Inventory of Executive Function; BRIEF) and emotional/behavioral problems (Child Behavior Checklist; CBCL). Linear mixed models tested the effect of sleep category and a group-by-sleep interaction on each measure, cross-sectionally and longitudinally.

Results

22qDel and 22qDup carriers both reported poorer sleep than controls, but did not differ from each other. Cross-sectionally and longitudinally, poor sleepers scored higher on all SIPS subdomains, CBCL subdomains (anxious/depressed, somatic complaints, thought problems, and aggressive behavior), as well as RBS and SRS total scores. There were significant group-by-sleep interactions for positive symptoms and the majority of CBCL subdomains, in which the difference between good and poor sleepers was larger in 22qDel compared to 22qDup.

Conclusions

Our findings indicate that CNVs at the 22q11.2 locus impact sleep which, in turn, influences psychopathology. Sleep disturbances can differentially impact psychopathology, depending on 22q11.2 gene dosage. Our findings serve as a starting point for exploring a genetic basis for sleep disturbance in developmental neuropsychiatric disorders.

Trial Registration

Not Applicable

Background

Disruptions in sleep quality and physiology are widely prevalent and impairing in individuals with developmental neuropsychiatric disorders, including autism spectrum disorder (ASD) [1], psychotic spectrum disorders [2, 3], and attention deficit hyperactivity disorder (ADHD) [1, 4]. Sleep has a complex, bidirectional relationship with psychiatric symptoms. For example, prolonged sleep deprivation can cause temporary perceptual distortions, disordered thinking, and hallucinations [5], while psychological distress related to psychosis worsens sleep quality and continuity. Further,

a behavioral sleep intervention can improve sleep, psychosis symptoms, and psychological distress [6, 7] in patients with psychotic illness. These sleep improvements were shown to mediate changes in hallucinations and paranoia [8]. In cross-sectional studies, sleep mediates the relationships between restrictive and repetitive behaviors and real-world executive function, [9] while in a study of boys with ASD, sleep disturbance was found to moderate the relationship between ASD symptom severity and problem behaviors [10]. Moreover, clinical trials of effective sleep interventions in children with neurodevelopmental disorders improved a range of behavioral and mood symptoms for at least six months post-treatment [11–13]. Taken together, these findings offer compelling evidence that sleep may be a modifiable treatment target for psychiatric disorders, making a deep understanding of the role of sleep in these disorders an area of critical research interest. However, the lack of longitudinal studies focused on elucidating mechanistic relationships limits our current understanding.

The vast heterogeneity within psychiatric diagnostic classifications and the complex relationship between sleep, environment, genetics, and neurobiology, pose a challenge in studying sleep's role in psychopathology. The gold-standard of measuring sleep, polysomnography (PSG), requires research participants to sleep in a lab, often for multiple nights, while wearing electroencephalography (EEG) and physiological sensors. This poses another challenge for sleep studies, particularly in pediatric and psychiatric populations. Therefore, self-report and parent-report questionnaires are often the most feasible way to measure sleep [14]; while these metrics have shown to correlate well with 'gold standard' laboratory-based measures [14], they cannot address the underlying biology critical for understanding sleep's role in psychopathology. One strategy to address these challenges is to take a "genetics-first" approach of studying individuals with a known genetic etiology, such as copy number variations (CNVs) that confer large effects on psychopathology risk. Dissecting sleep changes associated with CNVs could reveal genetic influences on sleep and the brain relevant to idiopathic disorders.

The 22q11.2 locus is a genomic hotspot with highly conserved genes critical to neurodevelopment [15]. CNVs in this locus (deletions or duplications) confer some of the greatest known risks of developmental neuropsychiatric disorders [16]. 22q11.2 deletion syndrome (22qDel; also known as DiGeorge Syndrome), a 1.5 to 2.6 megabase hemizygous deletion at this locus, is one of the most common genetic syndromes, occurring in up to 1 in ~4000 live births [17]. It is associated with congenital malformations, developmental delay (DD) and intellectual disability (ID), as well as multiple psychiatric disorders including ADHD, ASD, and anxiety disorders [18]. This deletion is also one of the greatest known risk factors for developing a psychotic disorder, with up to 20-fold increased risk [19–23] compared to the general population, and an approximately 10-fold increased risk compared to populations with other neurodevelopmental disorders [24].

Notably, a duplication in the 22q11.2 region (22qDup) also confers increased risk of developmental psychiatric disorders, but occurs ~2.5 times more frequently than a deletion [16]. Relative to the 22qDel, little is known about the 22qDup phenotype. Notably, however, several recent studies reported that 22qDup is associated with a significantly lower rate of schizophrenia compared to the general population, suggesting a potential gene-dosage effect of the 22q11.2 locus on schizophrenia risk [22, 25, 26]. Further 22q11.2 gene-dosage effects have been found for both brain structure [27] and neurocognitive profiles [28]. While both the 22qDel and 22qDup confer increased risk for neurodevelopmental disorders, they differentially modulate cognitive functioning and psychosis-related symptoms [28]. Similarly, while both 22q11.2 CNVs exhibit increased ASD symptomatology compared to controls, they displayed distinct ASD symptom profiles [28].

In addition, recent evidence suggests the 22qDel confers elevated rates of sleep problems [29–32]. The proportion of 22qDel carriers with clinically significant sleep problems has been reported to range from 60-97% [30, 31]. Relative to controls, subjects with 22qDel report increased sleep latency, nighttime waking, sleep anxiety, sleep-disordered

breathing, daytime sleepiness and decreased sleep duration and quality [29–32]. These sleep disturbances were associated with cognitive and immune dysfunction, ADHD, and anxiety disorders [29, 30]. To our knowledge, no studies have yet investigated sleep disturbance associated with 22qDup. Little is known about sleep and its effect on psychiatric symptomatology in reciprocal 22q11.2 CNVs, and the current literature is limited by small sample sizes at a single timepoint. Given the high rate of sleep disturbances and neurodevelopmental disorders, and the opportunity to study gene dosage effects, investigation of reciprocal 22q11.2 CNVs offers a rich opportunity to learn about the mechanisms of sleep disturbance relevant to psychiatric disorders.

Our study aimed to address these gaps and to serve as a starting point for understanding biological underpinnings of sleep's role in psychopathology by characterizing sleep and its effect on psychiatric symptoms in the largest known cohort of reciprocal 22q11.2 CNV carriers. First, we examined the prevalence and severity of self-reported sleep disturbance in 22qDel and 22qDup carriers compared to controls at baseline and longitudinally over one year. Next, we compared sleep disturbance between the three subject groups and controlled for medications and psychiatric comorbidities, to determine if sleep disturbance is an independent feature of 22q11.2 CNVs. Lastly, we assessed the relationship of sleep to developmental psychiatric symptoms and neurobehavioral traits cross-sectionally and longitudinally over one year, and tested for differences in these relationships between CNV groups.

Materials And Methods

Participants

The total sample consisted of 237 participants: 107 with a molecularly confirmed 22q11.2 deletion, 42 with a confirmed 22q11.2 duplication, and 88 healthy controls. All groups were age and sex- matched (see Table 1 for sample demographics). Participants were a subset of those recruited for an ongoing longitudinal study conducted at University of California at Los Angeles. The majority of participants in this study were included in previous cross-sectional studies reporting on different research questions [27, 28]. For the longitudinal portion of the present study, only the first two study timepoints were included, as maximal data were available. Patients were recruited from local clinics, national support groups, and other online avenues. Control participants were recruited from the same communities as CNV carriers through online postings, local schools, pediatric clinics, and other locations in the community.

Participants with significant neurological or medical conditions (unrelated to 22q11.2 CNVs) affecting brain structure or function, previous head trauma with loss of consciousness, insufficient English fluency, and/or substance abuse/dependence within the past six months were excluded. All participants gave verbal and written informed consent to participate in the study. Participants under 18 years of age provided written assent and their parent/guardian provided written consent. The University of California at Los Angeles Institutional Review Board approved all study procedures and documents.

Assessments

Developmentally appropriate clinical and cognitive assessments were administered to all participants. Supervised clinical psychology doctoral students administered structured psychodiagnostic evaluations to assess for psychiatric diagnoses. All diagnoses were determined by trained clinicians who participated in ongoing quality assurance and case consensus procedures. Training, reliability, and quality assurance procedures for psychodiagnostic assessments and clinician rating scales are detailed in prior publications [28, 33].

To study the relationship between sleep and clinical symptoms and neurobehavioral traits, we selected assessments measuring traits and behaviors associated with sleep in other clinical populations including schizophrenia and ASD. For each assessment, we first tested if there was an effect of sleep on the measure's global score. If there was a significant ($q < 0.05$) or marginally significant effect ($q < 0.1$) of sleep, the measure was broken down into its subscales to test for differential effects between subdomains of each trait measure.

Psychosis-Relevant Measures. The Structured Interview for Psychosis-Risk Syndromes (SIPS) [34], a clinician-rated semi-structured interview, was used to measure psychosis-risk symptoms including positive, negative, disorganized, and general symptoms. Participants over the age of ten completed the SIPS interview, administered by a trained clinician.

Autism Spectrum Measures. We chose to assess repetitive behaviors and social deficits because both of these domains are associated with sleep in studies of idiopathic ASD [9, 12, 13, 35–37]. The Repetitive Behavior Scale (RBS) [38] is a parent-report scale used to measure stereotyped, self-injurious, restrictive, need for sameness, compulsive, and ritualistic behaviors. A higher score on the RBS subscales indicates an increased frequency of behaviors. To measure social communication deficits, we used the Social Responsiveness Scale-2nd edition (SRS) [39], a parent-report rating scale measuring dysfunctional social behavior with the subdomains: awareness, cognition, communication, autistic traits, and motivation. Further information on scoring methods are detailed in Jalal et al. 2021 [40].

Real-World Executive Function. The Behavior Rating Inventory of Executive Function [41] (BRIEF) was used to measure parent-reported real-world executive function in participants aged 6-18. A previous study in a population-based cohort found associations between sleep, autistic traits, and the BRIEF [9], making it a measure of interest for the present study. The BRIEF consists of an overall global composite score and eight clinical subscales including: shifting, emotional, monitoring, inhibition, plan/organize, and organization/material.

Emotional or Behavioral Problems. We also investigated the relationship between sleep and emotional or behavioral problems on the Child Behavior Checklist (CBCL) [42, 43]. The CBCL subdomains are anxious/depressed, withdrawn/depressed, somatic complaints, social problems, attention problems, rule breaking, aggressive behavior, and thought problems. The CBCL was completed by the parents of participants aged 6-18.

Sleep Measure. To measure sleep disturbance on a continuous scale, we used item G1 from the SIPS (SIPSG1), which rates level of sleep disturbance on a six-point scale. A rating of six corresponds with severe sleep disturbance. The SIPS has not been validated in children under the age of 10, therefore analyses using this variable did not include participants younger than 10. To include the entire age range of our cohort in analyses of sleep effects on psychiatric symptoms, we created a categorical variable which classified participants as either good or poor sleepers. Previous studies in children with developmental psychiatric disorders have validated the use of a categorical variable based on parent-reported sleep using sleep questionnaires, actigraphy, and PSG [36, 44]. Participants 10 years and older were classified as poor sleepers if they scored a 3 or higher on SIPSG1. Participants 10 years or younger were classified as a poor sleeper if they scored 2 on the CBCL checklist item 100 (CBCL100). CBCL100 asked parents to rate their child's trouble sleeping on a scale from 0-2 (not true to very true or often true). The comparability of this categorical sleep variable was verified through correlations between the CBCL100 and SIPSG1 (see Supplementary Figure 1, Supplementary Tables 1-2) and sensitivity analyses which exclude subjects who did not complete the SIPS (see Supplementary Figures 2-3 and Supplementary Tables 3-4). CBCL100 and SIPSG1 were removed from total scores on the SIPS and CBCL. CBCL100 has been validated to be concordant with sleep questionnaires, sleep diaries, actigraphy and PSG [45, 46] while SIPSG1 has been used to measure sleep disturbance in numerous studies of individuals at high-risk for developing a psychotic disorder [47–49]

Statistical Analyses

All statistical analyses were performed, and figures created, in R 4.0.2 [50] using the packages lme4 [51] and ggplot2 [52]. To address the question of how sleep disturbance in reciprocal 22q11.2 CNV carriers compares to controls, we conducted linear mixed models with sleep as the dependent variable (using the continuous variable) and participant group (22qDel vs. 22qDup vs. control, with control as the reference group) as the independent variable. We analyzed each model cross-sectionally (at baseline) and longitudinally (two timepoints across approximately one year). The longitudinal model included a group-by-time interaction. All models included age and biological sex as covariates and participant ID as the random effects term. To test for differences between CNV groups, we re-ran the same models including only participants in the CNV groups (22qDel as the reference group). To determine if differences in sleep between CNV groups and controls could be attributed to differences in psychiatric comorbidities or medications between groups, we independently added variables measuring attention, current medication, Full Scale IQ, ASD diagnosis, and psychotic disorder diagnosis into the models to test if the group difference remained statistically significant when accounting for these variables. Within each model, a False Discovery Rate (FDR) correction was applied on the effects of subject group.

To test the relationship between sleep disturbance and clinical symptoms, we conducted linear mixed models with each symptom domain as the dependent variable and the sleep categorization (good vs. poor sleeper) and participant group (22qDel vs. 22qDup; 22qDel as the reference group) as independent variables. Cross-sectional models included a group-by-sleep interaction and longitudinal models included a group-by-time interaction. All models included age and biological sex as covariates and participant ID as the random effects term. Due to small number of poor sleepers in the control group, only CNV carriers were included in analyses of psychiatric symptoms. To control for multiple comparisons within each domain, FDR correction was applied. Only the main effects of sleep, group, and group-by-sleep interaction were included in the FDR correction, since effects of time, age, and sex are not the primary variables of interest in this study. A q-value <0.05 was considered statistically significant.

Results

Participant Demographics

Demographic variables for each group at each timepoint are reported in Table 1. As expected, both 22qDel and 22qDup groups showed significantly elevated rates of ASD diagnoses and medication use at both timepoints compared to controls. Consistent with previous literature [25], 22qDel reported significantly higher rates of psychotic disorders compared to the other two groups. There was also a significant difference in highest parental education level between the 22qDel and 22qDup group.

Table 1
Demographic and clinical characteristics at baseline and one-year follow-up

Baseline	Typically Developing Control Subjects	22q11.2 Deletion Carriers	22q11.2 Duplication Carriers
n_{total}	88	107	42
n_{SIPS}	74	85	34
Age, Years (SD)	14.65 (7.4)	14.56 (8.0)	16.26 (13.1)
Age Range, Years	6-45	6-43	5-49
Males, n (%)	41 (47.1%)	53 (50.0%)	23 (54.8%)
Non-white, n (%) ^{a,b}	27 (30.7%)	10 (9.3%)	1 (2.4%)
Highest Parental Education, Years (SD) ^c	16.78 (3.3)	17.17 (2.5)	15.41 (2.7)
Poor Sleepers, n (%) ^{d,e}	3 (3.4%)	34 (31.8%)	14 (33.3%)
Psychosis, n (%) ^{c,d}	0 (0%)	12 (11.2%)	0 (0%)
ASD, n (%) ^{d,e}	0 (0%)	48 (44.9%)	17 (40.5%)
Medication, n (%) ^{d,e}			
Anti-Psychotics	0	13 (12.1%)	4 (9.5%)
Mood Stabilizers	2 (2.3%)	12 (11.4%)	3(7.1%)
Stimulants	2 (2.3%)	3 (2.9%)	6 (14.3%)
Other Medication	1 (1.1%)	8 (7.6%)	2 (4.8%)
No Medication	83 (94.3%)	69 (65.7%)	27 (64.3%)
One Year Follow-Up			
n_{total}	42	62	20
n_{SIPS}	32	52	17
Age, Years (SD)	14.12 (5.9)	16.18 (7.2)	14.55 (9.1)
Age Range, Years	7-30	7-41	6-44
Males, n (%)	18 (43.9%)	27 (43.5%)	13 (65.0%)

ASD, autism spectrum disorder. n_{SIPS} , number of subjects included in analyses of SIPs sleep variable

^a Control > 22qDel ($p<0.05$)

^b Control > 22qDup ($p<0.05$)

^c 22qDel > 22qDup ($p<0.05$)

^d 22qDel > Control ($p<0.05$)

Baseline	Typically Developing Control Subjects	22q11.2 Deletion Carriers	22q11.2 Duplication Carriers
Non-white, <i>n</i> (%)	8 (19.0%)	9 (14.5%)	1 (5.0%)
Highest Parental Education, Years (SD)	17.86 (2.9)	17.00 (2.2)	15.42 (3.1)
Poor Sleepers, <i>n</i> (%) ^{d,e}	1 (2.4%)	19 (30.6%)	7 (35.0%)
Psychosis, <i>n</i> (%)	0 (0%)	6 (9.8%)	0 (0%)
ASD, <i>n</i> (%) ^{d,e}	0 (0%)	22 (36.1%)	9 (45.0%)
Medication, <i>n</i> (%) ^{d,e}			
Anti-Psychotic	1 (2.4%)	8 (13.1%)	0 (0%)
Mood Stabilizer	1 (3.2%)	7 (11.5%)	6 (30.0%)
Stimulants	2 (4.9%)	3 (4.9%)	1 (5.0%)
Other Medication	0 (0%)	4 (6.6%)	1 (5.0%)
No Medication	37 (90.2%)	39 (63.9%)	12 (60.0%)
ASD, autism spectrum disorder. <i>n</i> _{SIPS} , number of subjects included in analyses of SIPS sleep variable			
^a Control > 22qDel (<i>p</i> <0.05)			
^b Control > 22qDup (<i>p</i> <0.05)			
^c 22qDel > 22qDup (<i>p</i> <0.05)			
^d 22qDel > Control (<i>p</i> <0.05)			

^e 22qDup > Control (*p*<0.05)

Comparison of Sleep Disturbance Between 22q11.2 CNV Carriers and Controls

Both 22q11.2 deletion and duplication groups reported significantly greater sleep disturbance on the SIPS compared to controls, cross-sectionally and longitudinally (Figure 1, Table 2). Sleep disturbance severity was not statistically different between 22qDel and 22qDup in either model (cross-sectional: *b*=0.015, *q*=0.940; longitudinal: *b*=0.006, *q*=0.982). These results are summarized in Table 2. About one-third of both CNV groups at each timepoint met the poor sleeper criteria, while <4% of controls met these criteria (Table 1).

As shown in Table 2, the differences in the continuous sleep measure between CNV groups and controls remained significant when medication, attention, ASD diagnosis, and psychotic disorder diagnosis were each added to the models. Both cross-sectionally and longitudinally, subjects on antipsychotics reported greater sleep disturbance compared to those on no medication. Across groups at each timepoint, there was a main effect of attention on sleep such that individuals with more attention problems reported worse sleep disturbance. The effect of ASD and the effect of psychotic disorders on sleep disturbance did not reach significance. There were no significant differences in sleep between CNV groups when medication, attention, ASD diagnosis, and psychotic disorder diagnosis were included in the models.

When IQ was added to both models, the difference in sleep between 22qDel and controls remained significant, but the difference between 22qDup and controls was attenuated to a trend level (Table 2). There remained no significant differences in sleep disturbance severity between CNV groups when IQ was added to the model.

Table 2
Differences in SIPS-measured Sleep Disturbance between subject groups

Covariates	Effect of Time		Effect of Covariate		Effect of Subject Group			Group * Time Interaction		
Cross-sectional	β	<i>p-value</i>	<i>Group</i>	β	<i>p-value</i>	<i>Group</i>	β	<i>q-value</i>	β	<i>p-value</i>
Age + Sex	-	-	-	-	-	Del	0.728	<0.001	-	-
				-	-	Dup	0.741	<0.001	-	-
Age+ Sex + Attention	-	-	-	0.222	0.015	Del	0.525	0.009	-	-
			-			Dup	0.592	0.014	-	-
Age+ Sex + Medication	-	-	Antipsychotic	0.557	0.026	Del	0.580	<0.001	-	-
			Mood Stabilizer	0.242	0.354	Dup	0.675	<0.001	-	-
			Stimulant	-0.027	0.932	-	-	-	-	-
			Other	0.521	0.107	-	-	-	-	-
Age + Sex + IQ	-	-	-	-0.128	0.244	Del	0.516	0.026	-	-
						Dup	0.500	0.070	-	-
Age + Sex + ASD	-	-	-	0.033	0.643	Del	0.782	<0.001	-	-
						Dup	0.811	0.001	-	-
Age + Sex + PSY	-	-	-	0.558	0.054	Del	0.648	<0.001	-	-
						Dup	0.743	<0.001	-	-
Longitudinal	β	<i>p-value</i>	<i>Group</i>	β	<i>p-value</i>	<i>Group</i>	β	<i>q-value</i>	β	<i>p-value</i>
Age + Sex	-0.074	0.754	-	-	-	Del	0.747	<0.001	-0.122	0.601
						Dup	0.747	<0.001	-0.325	0.289
Age+ Sex + Attention	-0.214	0.276	-	0.222	0.003	Del	0.546	0.005	0.023	0.927
						Dup	0.611	0.010	-0.273	0.421
Age+ Sex + Medication	-0.074	0.690	Antipsychotic	0.537	0.013	Del	0.600	<0.001	-0.106	0.654
			Mood Stabilizer	0.321	0.109	-	-	-	-	-
			Stimulant	0.110	0.657	-	-	-	-	-

^a Insufficient longitudinal IQ data in 22q11.2 duplication group

Covariates	Effect of Time		Effect of Covariate		Effect of Subject Group			Group * Time Interaction	
			Other	0.430	0.099	Dup	0.662	<0.001	-0.363 0.261
Age + Sex + IQ ^b	-0.196	0.312	-	-0.102	0.299	Del	0.574	0.011	-0.130 0.595
						Dup	0.522	0.056	- -
Age + Sex + ASD	-0.061	0.740	-	-0.048	0.387	Del	0.669	<0.001	-0.085 0.725
						Dup	0.647	0.005	-0.312 0.314
Age + Sex + PSY	-0.055	0.767	-	0.305	0.118	Del	0.703	<0.001	-0.120 0.615
						Dup	0.748	<0.001	-0.381 0.229
^a Insufficient longitudinal IQ data in 22q11.2 duplication group									

Effect of Sleep on Psychosis-Risk Symptoms

Across CNV groups, poor sleepers reported more severe positive, negative, disorganized, and general psychosis-risk symptoms than good sleepers, both cross-sectionally (Table 3) and longitudinally (Table 4), as shown in Figure 2. There was a significant group-by-sleep interaction for positive symptoms at baseline (Figure 3). There was a bigger difference in positive symptoms between good and poor sleepers in the 22qDel group compared to the 22qDup group. 22qDel subjects reported higher severity of negative symptoms, both cross-sectionally and longitudinally, and a higher severity of positive and disorganized psychosis-risk symptoms longitudinally compared to 22qDup.

Effect of Sleep on Autism-Related Symptoms

There was a significant effect of sleep categorization on total RBS and total SRS scores at baseline (Table 3, Supplementary Figures 4-5) and across timepoints (Table 4; Supplementary Figures 4-5). Poor sleepers, across CNV groups, reported more frequent self-injurious and ritualistic behaviors on the RBS at baseline and across timepoints (Supplementary Figure 4). Poor sleepers also reported increased frequency of restrictive and need for sameness behaviors at baseline only. There were no statistically significant effects of sleep on the stereotyped and compulsive behavior subscales. No effects of sleep on SRS subscales survived FDR correction cross-sectionally (Supplementary Figure 5). Longitudinally, poor sleepers scored significantly higher (i.e., more pathological) on the aware, cognition, communication, and autistic traits subscales of the SRS. There was no significant effect of sleep on the motivation subscale.

Effect of Sleep on Real-World Executive Functions

Poor sleepers, across CNV groups, scored worse on the global composite overall index on the BRIEF, both cross-sectionally (Table 3) and longitudinally (Table 4), although the effect of sleep in the cross-sectional model was marginally significant. There was a significant main effect of sleep categorization, in which poor sleepers scored higher (i.e. more pathological), on the shift, emotional control, monitor, and working memory subscales longitudinally, but not cross-sectionally (Supplementary Figure 6). The effects of sleep on inhibition, plan/organize, organization/material, or initiate subscales did not reach significance in the cross-sectional nor the longitudinal model.

Effect of Sleep on Behavioral or Emotional Problems

Cross-sectionally across CNV groups, poor sleepers scored significantly higher on all subdomains of the CBCL (Table 3, Figure 4). There were significant group-by-sleep interactions on all subdomains except anxious/depressed, such that there was a larger difference between good and poor sleepers in 22qDel carriers compared to 22qDup carriers (Figure 3). Longitudinally, poor sleepers across CNV groups scored significantly higher on the anxious/depressed, somatic complaints, thought problems, and aggressive behaviors subdomains. Poor sleepers scored marginally higher than good sleepers on the attention subscale. There was a trend towards a main effect of group in which the 22qDel group scored higher than the 22qDup group on somatic complaints and thought problems.

Table 3
Results of cross-sectional models

	Effect of Sleep		Effect of CNV Group		Group*Sleep Interaction	
	β	<i>q-value</i>	β	<i>q-value</i>	β	<i>q-value</i>
Psychosis-Risk Symptoms (SIPS)						
Positive Symptoms	0.976	<0.001	-0.348	0.180	-0.855	0.041
Negative Symptoms	0.502	0.041	-0.659	0.028	-0.223	0.570
General Symptoms	0.860	<0.001	-0.358	0.180	-0.505	0.234
Disorganized Symptoms	0.838	<0.001	-0.040	0.871	-0.546	0.234
Repetitive Behavior Scale (RBS)	β	<i>q-value</i>	β	<i>q-value</i>	β	<i>q-value</i>
Total Repetitive Behaviors	0.657	0.008	0.322	0.415	-0.447	0.299
Stereotyped Behaviors	0.123	0.721	0.715	0.014	0.206	0.721
Self-Injurious Behaviors	0.762	0.010	0.104	0.769	-0.300	0.721
Compulsive Behaviors	0.492	0.078	0.052	0.827	-0.139	0.749
Ritualistic Behavior	0.593	0.036	0.235	0.562	-0.188	0.721
Sameness Behavior	0.582	0.036	0.374	0.415	-0.763	0.163
Restrictive Behavior	0.623	0.036	0.168	0.666	-0.644	0.227
Social Responsiveness Scale (SRS)	β	<i>q-value</i>	β	<i>q-value</i>	β	<i>q-value</i>
Total SRS Score	0.535	0.037	0.140	0.852	-0.149	0.728
Aware	0.518	0.105	0.115	0.852	-0.262	0.737
Cognition	0.462	0.105	0.054	0.852	-0.179	0.737
Communication	0.516	0.105	0.232	0.852	-0.145	0.737
Motivation	0.445	0.105	0.044	0.852	-0.300	0.737
Autistic Traits	0.444	0.105	0.094	0.852	0.144	0.737
Real-World Executive Function (BRIEF)	β	<i>q-value</i>	β	<i>q-value</i>	β	<i>q-value</i>
Global Composite	0.508	0.058	0.251	0.698	-0.027	0.951
Inhibition	0.301	0.329	0.332	0.698	0.190	0.858
Shifting	0.531	0.147	0.259	0.698	0.109	0.858
Emotional	0.548	0.147	0.276	0.698	0.058	0.891
Initiate	0.343	0.296	0.189	0.778	-0.661	0.296
Working Memory	0.436	0.214	-0.120	0.801	0.255	0.858
Plan/Organize	0.362	0.296	-0.113	0.801	-0.118	0.858
Organization/Materials	0.306	0.329	0.031	0.899	0.110	0.858
Monitor	0.467	0.177	0.086	0.801	0.124	0.858

	Effect of Sleep		Effect of CNV Group		Group*Sleep Interaction	
Emotional or Behavioral Problems (CBCL)	β	<i>q-value</i>	β	<i>q-value</i>	β	<i>q-value</i>
Anxious/Depressed	0.876	0.003	-0.086	0.927	-0.836	0.083
Withdrawn/Depressed	0.738	0.007	-0.022	0.927	-1.143	0.020
Somatic Complaints	0.943	<0.001	-0.149	0.927	-1.370	0.007
Social Problems	0.737	0.007	0.048	0.927	-1.183	0.017
Thought Problems	1.420	<0.001	-0.184	0.927	-1.105	0.012
Attention Problems	0.795	0.006	0.147	0.927	-1.342	0.009
Rule Breaking	0.617	0.017	-0.076	0.927	-1.438	0.006
Aggressive Behavior	1.203	<0.001	0.261	0.927	-1.483	0.004

Table 4
Results of longitudinal models

	Effect of Sleep		Effect of CNV Group		Effect of Time		Group*Time Interaction	
Psychosis-Risk Symptoms	β	<i>q-value</i>	β	<i>q-value</i>	β	<i>p-value</i>	β	<i>p-value</i>
Positive Symptoms	0.706	<0.001	-0.675	<0.001	-0.207	0.005	0.044	0.750
Negative Symptoms	0.426	0.019	-0.734	<0.001	-0.119	0.277	0.574	0.009
General Symptoms	0.710	<0.001	-0.245	0.203	-0.186	0.164	-0.051	0.844
Disorganized Symptoms	0.575	0.003	-0.540	0.009	-0.054	0.631	0.160	0.473
Repetitive Behavior Scale (RBS)	β	<i>q-value</i>	β	<i>q-value</i>	β	<i>p-value</i>	β	<i>p-value</i>
Total Repetitive Behaviors	0.407	0.030	0.191	0.800	0.005	0.963	-0.021	0.936
Stereotyped Behaviors	0.144	0.382	0.760	<0.001	0.051	0.715	-0.05	0.093
Self-Injurious Behaviors	0.457	0.037	0.008	0.970	0.024	0.844	0.141	0.596
Compulsive Behaviors	0.350	0.103	0.014	0.970	0.032	0.783	-0.090	0.722
Ritualistic Behavior	0.468	0.037	0.192	0.800	0.059	0.629	-0.073	0.784
Sameness Behavior	0.261	0.207	0.156	0.800	-0.068	0.539	0.147	0.542
Restrictive Behavior	0.381	0.076	-0.013	0.970	0.040	0.758	0.006	0.983
Social Responsiveness Scale (SRS)	β	<i>q-value</i>	β	<i>q-value</i>	β	<i>p-value</i>	β	<i>p-value</i>
Total SRS Score	0.453	0.015	0.087	0.971	-0.104	0.272	0.268	0.203
Aware	0.445	0.029	0.024	0.971	0.110	0.330	0.190	0.449
Cognition	0.429	0.029	-0.007	0.971	-0.096	0.359	0.204	0.380
Communication	0.424	0.029	0.177	0.971	-0.136	0.155	0.206	0.331
Motivation	0.243	0.185	-0.028	0.971	-0.182	0.084	0.450	0.055
Autistic Traits	0.467	0.029	0.115	0.971	-0.047	0.600	0.167	0.402
Real-World Executive Function (BRIEF)	β	<i>q-value</i>	β	<i>q-value</i>	β	<i>p-value</i>	β	<i>p-value</i>
Global Composite	0.405	0.028	0.205	0.702	-0.214	0.040	0.319	0.165
Inhibition	0.275	0.150	0.380	0.405	-0.036	0.665	0.178	0.331
Shifting	0.442	0.042	0.329	0.405	-0.048	0.649	0.214	0.361
Emotional	0.511	0.032	0.290	0.405	-0.260	0.004	0.293	0.135
Initiate	0.130	0.462	-0.002	0.993	-0.180	0.172	0.036	0.900
Working Memory	0.406	0.049	-0.030	0.993	-0.259	0.026	0.270	0.286
Plan/Organize	0.293	0.150	-0.175	0.713	-0.170	0.158	0.452	0.089

	Effect of Sleep		Effect of CNV Group		Effect of Time		Group*Time Interaction	
Organization/Materials	0.280	0.150	0.054	0.992	-0.175	0.063	0.225	0.274
Monitor	0.469	0.032	0.132	0.753	-0.268	0.012	0.530	0.023
Emotional or Behavioral Problems (CBCL)	<i>β</i>	<i>q-value</i>	<i>β</i>	<i>q-value</i>	<i>β</i>	<i>p-value</i>	<i>β</i>	<i>p-value</i>
Anxious/Depressed	0.619	0.005	-0.305	0.237	-0.200	0.247	0.067	0.840
Withdrawn/Depressed	0.355	0.082	-0.328	0.237	-0.348	0.049	0.203	0.543
Somatic Complaints	0.461	0.038	-0.511	0.064	-0.266	0.129	0.664	0.047
Social Problems	0.362	0.081	-0.270	0.282	-0.194	0.314	-0.020	0.958
Thought Problems	1.038	<0.001	-0.490	0.064	0.049	0.763	0.135	0.661
Attention Problems	0.421	0.061	-0.202	0.401	-0.253	0.149	0.194	0.560
Rule Breaking	0.247	0.195	-0.448	0.101	0.080	0.675	0.009	0.980
Aggressive Behavior	0.677	0.002	-0.100	0.624	-0.011	0.947	0.010	0.974

Discussion

In this study, we report several novel findings related to sleep and psychiatric symptomatology in 22q11.2 CNV carriers. First, similar to 22qDel, 22qDup was associated with more severe sleep disturbances than typically developing controls. Second, we found these sleep disturbances were independent of psychiatric conditions and medication usage. Third, sleep difficulties negatively impacted psychiatric symptomatology in both 22qDel and 22qDup carriers. Fourth, sleep disturbance had a differential impact on particular psychiatric symptoms in 22q11.2 CNV carriers; specifically, positive psychosis-risk symptoms, withdrawn/depressed symptoms, somatic complaints, social problems, thought problems, attention problems, rule breaking, and aggressive behavior. Lastly, we found differences in reported psychiatric symptomatology between 22q11.2 CNV carriers. The 22qDel group had higher levels of psychosis-risk symptoms, somatic complaints, and thought problems, while the 22qDup was associated with more stereotyped behaviors.

We found 22q11.2 CNV carriers reported significantly poorer sleep than controls, cross-sectionally and longitudinally, even when controlling for psychiatric comorbidities and medications, suggesting sleep disturbance is an independent feature of 22q11.2 CNVs. There was no difference in reported sleep disturbance between the two CNV groups. Increased sleep difficulty in 22qDel has been reported in previous cross-sectional studies [29–32]. In our study, about one-third of subjects in both the 22qDel and 22qDup groups were classified as poor sleepers, while prevalence rates of clinically significant sleep problems was previously reported to be greater than 60% in 22qDel carriers [30, 31]. This discrepancy could be attributed to different questionnaires used to classify significant sleep problems, and differing age groups. Our study reports on a cohort with a wide age range, which includes older adult participants, while previous studies focused exclusively on children. This is the first study to investigate sleep disturbance in 22qDup carriers, so there is no data to compare with our cohort.

Across CNV groups, poor sleepers reported elevated psychiatric symptomatology relative to good sleepers. Poor sleep had a consistently strong effect across psychosis-risk symptom subscales (SIPS) and emotional and behavior problems reported on the CBCL, similar to findings observed in idiopathic psychiatric disorders [47, 53]. This finding is

also consistent with and builds upon prior literature in 22qDel carriers, which found poor sleep is associated with anxiety disorders, ADHD, and conduct disorders [30]. Poor sleep had a varying impact on subdomains of ASD-related measures (RBS, SRS) and real-world executive function (BRIEF), such that sleep greatly impacted some subscales and had no significant effect on others. Previous studies in idiopathic ASD found poor sleepers scored higher on ritualistic and compulsive subscales of the RBS compared to good sleepers with ASD [44]. Further, sleep fragmentation was associated with RBS total score and ritualistic, compulsive, need for sameness, and restricted behaviors. Our findings in 22q11.2 CNV carriers are mostly consistent with this finding, except we did not find a significant effect of sleep on compulsive behaviors in either model. Consistent with previous findings in idiopathic ASD [54], we found total SRS score was significantly associated with sleep cross-sectionally and longitudinally, with poorer sleep associated with elevated SRS scores over time. While no SRS subscales were significantly associated with sleep at baseline, all SRS subscales except motivation was associated with sleep across timepoints. Our finding of a significant effect of sleep on BRIEF global composite is supported by a previous study reporting sleep deficits were associated with a worse global composite score on the BRIEF [9]. Contrary to expectations, the effect of sleep on BRIEF subscales did not reach significance at baseline. Longitudinally shifting, working memory, emotional, and monitor subscales were significantly associated with sleep. The discrepancy between cross-sectional and longitudinal findings on measures of real-world executive function and reciprocal social behavior (the BRIEF and the SRS, respectively) could be attributed to multiple factors. Statistically, it is possible that, despite some participant drop-out at the one-year follow-up, the longitudinal model is better powered to detect effects of sleep across timepoints, due to the addition of the within-subject follow-up data. Theoretically, it is also possible that the SRS and BRIEF measures are not impacted by acute poor sleep, but instead chronic poor sleep over an extended period of time affects these processes.

We found sleep has a greater effect on psychiatric symptomatology – namely, positive psychosis-risk symptoms, and withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule breaking, and aggressive behaviors - in 22qDel carriers relative to 22qDup carriers. This suggests 22qDel carriers are more susceptible to the effects of poor sleep compared to 22qDup, which is consistent with the fact that the 22qDel often confers a more severe phenotype compared to the 22qDup [16]. This finding is also consistent with recent cross-sectional findings from our group that the 22qDel has a greater effect on IQ, psychosis-risk symptoms, and brain morphometry compared to the 22qDup [27, 28]. The differential impact of sleep on psychiatric symptoms in 22q11.2 CNV carriers suggests that gene dosage at the 22q11.2 locus may influence mechanisms involved in sleep's relationship with symptoms of developmental psychiatric disorders. Further, it provides evidence for a genetic-basis of sleep disturbance in 22q11.2 CNVs, and perhaps idiopathic disorders, such as schizophrenia and ASD. This conclusion is supported by a recent study of the 22q11.2 locus in *drosophila*, which found knockout of the LZTR1 homolog gene on the 22q11.2 locus caused widespread sleep disturbance [55]. Further experiments revealed this gene affects sleep through GABAergic signaling, disruptions in which are also implicated in schizophrenia and ASD [56–60]. Taken together, these results suggest a genetic basis for sleep disturbance in 22q11.2 CNV carriers and associated psychiatric disorders. Further studies are required, in both humans and animal models, in order to identify underlying genetic and neurobiological mechanisms of sleep in 22q11.2 CNV carriers and determine how 22q11.2 genes impact the relationship between sleep and psychiatric symptoms, and if genes within this locus could contribute to sleep's role in idiopathic disorders. Future studies should include measures of brain circuitry, sleep physiology, and gene expression.

In addition to studying the association between sleep and 22q11.2 CNVs, we also report a number of group differences between 22qDel and 22qDup carriers that have not previously been reported. First, as in Lin et al [28], we found decreased stereotyped behaviors and increased positive and negative psychosis-risk symptoms in 22qDel carriers compared to 22qDup carriers. Expanding upon this finding, we also found 22qDel carriers reported more severe disorganized -but not general - psychosis-risk symptoms compared to 22qDup. On the CBCL, there was a trend

towards a significant group difference in thought problems and somatic complaints. 22qDel carriers reported more thought problems than 22qDup carriers, which is consistent with increased rates of psychotic disorders in 22qDel carriers and decreased rates in 22qDup carriers [19–23, 25, 26]. Additionally, 22qDel carriers reported more somatic complaints, which could be attributed to increased medical problems reported in this population.

In addition to contributing to the mechanistic understanding of the relationship between sleep and psychopathology, our findings also inform clinical knowledge of treating psychiatric symptoms in 22q11.2 CNV carriers. Our study suggests that an intervention that directly targets sleep could have multiple beneficial effects, with downstream influences on psychiatric symptoms and behavioral problems across diagnostic classifications in 22q11.2 CNV carriers. Further research is needed to test the effectiveness of individual sleep treatments in this population. Potential lines of study include clinical trials in 22q11.2 CNV carriers of behavioral sleep therapies, which have been effective in psychotic populations [6, 61], and melatonin, which has been effective in ASD populations [12, 13]. These clinical trials should not only test the ability of an intervention to treat sleep disturbance, but also its impact on neuropsychiatric symptoms.

As with most studies of rare disorders, there are several limitations of this study to consider. We were unable to collect objective, laboratory-based measures of sleep and did not administer a comprehensive sleep questionnaire. For younger participants, sleep disturbance scores were collected via parent report. While we acknowledge the limitations of this measure, we found our two sleep measures were highly correlated. Further, a recent study found that parent-reported subjective sleep report was as valid as participant-reported subjective sleep report when compared to PSG recording [14]. However, it is important to consider that subjective sleep report and PSG-derived sleep measures capture two related but distinct sleep-related processes. While subjective sleep measures are valid, they do not capture information about sleep physiology and neurobiology, meaning we cannot make inferences about biological underpinnings of the observed relationships. Thus, our study focuses only on subjectively-reported sleep disturbance and does not make inferences about objective measures of sleep or sleep physiology. Further, the nature of our sleep variable does not indicate the type of sleep disturbance exhibited, only its presence and severity. 22q11.2 CNVs are associated with craniofacial abnormalities, which can lead to increased rates of sleep-disordered breathing (SDB), such as obstructive sleep apnea [62, 63]. Sleep disturbance related to SDB confers a different clinical phenotype and affects downstream mechanisms differently than a sleep disturbance related to insufficient sleep [64, 65]. While it is possible that the observed difference in sleep disturbance between 22q11.2 CNV carriers and controls could be driven by higher rates of SDB in 22q11.2 CNV carriers, rates of airway problems and/or craniofacial abnormalities did not differ between poor sleepers and good sleepers (see Supplementary Information), so it is unlikely that these medical conditions accounted for the increased rates of poor sleepers. Nevertheless, future investigation of 22q11.2 CNV carriers should consider the differential impacts of sleep breathing disorders and disorders of insufficient sleep on brain structure, psychiatric symptoms, and neurobehavioral traits.

Another limitation to consider is the small sample size of the 22qDup group compared to that of the 22qDel and control groups. Unlike 22qDel carriers, 22qDup carriers often are not identified through clinical genetic testing due to the highly variable phenotype and less frequent medical comorbidity [16], posing a recruitment challenge for this population. While the cohort of 22qDup included here is relatively modest, it is one of the largest cohorts reported in the literature to date.

Conclusions

In summary, our findings establish that the 22q11.2 locus impacts sleep which, in turn, associates with psychopathology. Further, sleep disturbances can differentially affect psychopathology, depending on gene dosage.

These results contribute to our understanding of psychiatric symptoms in 22q11.2 CNV carriers and offer a potential intervention target. Our findings serve as a starting point for exploring a genetic basis for sleep disturbance in neurodevelopmental psychiatric disorders.

Abbreviations

22qDel: 22q11.2 deletion; 22qDup: 22q11.2 duplication; ADHD: attention deficit hyperactivity disorder; ASD: Autism spectrum disorder; BRIEF: Behavior Rating Inventory of Executive Function; CBCL: Child Behavior Checklist; CBCL100: Child Behavior Checklist item 100; CNV: Copy Number Variation; DD: Developmental Delay; EEG: electroencephalography; FDR: False Discovery Rate; ID: Intellectual Disability; PSG: polysomnography; RBS: Repetitive Behavior Scale; SIPS: Structured Interview for Psychosis-Risk Symptoms; SIPSG1: Structured Interview for Psychosis-Risk Syndromes item G1; SRS: Social Responsiveness Scale;

Declarations

Ethics approval and consent to participate: All data were collected upon approval from the University of Los Angeles's Institutional Review Board.

Consent for publication: Not Applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare they do not have competing interests.

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Figures

Figure 1

Quantitative measure of sleep disturbance across groups. Sleep disturbance, assessed via the SIPS, is significantly worse in CNV carriers compared to controls cross-sectionally ($q < 0.001$) and longitudinally ($q < 0.001$). However, there is no significant difference in sleep quality between CNV groups ($q > 0.940$). Large dots represent the group mean and 95% confidence interval at each timepoint.

Figure 2

SIPS subdomain scores in good and poor sleepers at each timepoint within 22q11.2 CNV groups. There was a significant main effect of sleep category on positive ($q < 0.001$), negative ($q < 0.042$), disorganized ($q < 0.003$), and general symptoms ($q < 0.001$) cross-sectionally and longitudinally. Large dots represent the group mean and 95% confidence interval for good and poor sleepers at each timepoint.

Figure 3

Baseline CNV group-by-sleep interactions. There were significant group-by-sleep interactions at baseline for positive psychosis-risk symptoms ($q=0.041$), and CBCL-measured withdrawn/depressed ($q=0.020$), somatic complaints ($q=0.007$), social problems ($q=0.017$), thought problems ($q=0.012$), attention problems ($q=0.009$), rule-breaking ($q=0.006$), and aggressive behaviors subscales ($q=0.004$). Large dots represent the group mean and 95% confidence interval for good and poor sleepers in each subject group.

Figure 4

CBCL subdomain scores in good and poor sleepers at each timepoint within 22q11.2 CNV groups. At baseline, there was a significant main effect of sleep category on all CBCL subdomains ($q < 0.017$). Across timepoints, there was a significant main effect of sleep category on anxious/depressed ($q = 0.005$), somatic complaints ($q = 0.038$), thought problems ($q < 0.001$), and aggressive behavior ($q = 0.002$) subscales. There was a trend towards a significant effect of sleep category on attention problems ($q = 0.061$). Large dots represent the group mean and 95% confidence interval for good and poor sleepers at each timepoint.

Supplementary Files

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