

**ARE CHILDREN WITH FRAGILE X SYNDROME LOSING THEIR Zzzz's ... AND Y?**

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## ARE CHILDREN WITH FRAGILE X SYNDROME LOSING THEIR Zzzz's ... AND Y?

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University of Pittsburgh, 2008

**AIMS:** To investigate the potential associations between daily bedtime routines, evening fluctuations in parent mood, and sleep patterns for a sample of children with fragile X syndrome (FXS). This study also investigated whether the association among these factors varies dependent upon the severity of the genetic mutation. **SAMPLE:** Children ages 3 years, 0 months to 17 years, 11 months with a full or partial mutation of FXS (N = 95). **METHOD:** In-home assessments were completed including a demographic form, bedtime routine information sheet, and abbreviated *Child Sleep Habits Questionnaire (CSHQ)*, followed by a 14-day sleep diary. Actigraphy was added to the protocol for the local sample of participants (n = 7) from the Fragile X Center of Children's Hospital of Pittsburgh. **RESULTS:** Parents reported that 48% of their children with FXS have sleep problems at a level worthy of a sleep clinic referral; 20% of participants received medication to induce sleep, but 58% continued to score in the clinical range on the *CSHQ* despite receiving medications. Actigraphy showed children with FXS had significantly different sleep parameters than a control group (n = 14). Caregiver mood was a significant correlate of sleep disturbances; children with FXS whose caregivers reported feeling more overwhelmed or poorer mood had more sleep disturbances. Inconsistent bedtime routine was also associated with sleep disturbances. **CONCLUSIONS:** These data strongly suggest that routine clinical care of children with FXS should include careful screening of sleep. Interventions to assist parents in establishing and/or maintaining bedtime routines and managing their mood may be warranted. Effective use of medication to enhance sleep requires further investigation. Additional research is needed to identify specific problems with sleep so that clinical trials focusing on key parameters can be initiated.

## TABLE OF CONTENTS

<b>PREFACE.....</b>	<b>IX</b>
<b>1.0 INTRODUCTION.....</b>	<b>1</b>
<b>2.0 LITERATURE REVIEW.....</b>	<b>3</b>
<b>2.1 A SYNOPSIS OF FRAGILE X SYNDROME.....</b>	<b>3</b>
<b>2.1.1 Prevalence, Etiology, and Clinical Presentation .....</b>	<b>5</b>
<b>2.2 SLEEP PATTERNS IN TYPICALLY DEVELOPING CHILDREN.....</b>	<b>7</b>
<b>2.2.1 A Brief Tour of Sleep Architecture .....</b>	<b>7</b>
<b>2.2.2 Classification of Sleep Disorders .....</b>	<b>9</b>
<b>2.2.3 Typical Assessment of Sleep Disorders.....</b>	<b>11</b>
<b>2.2.4 Prevalence of Sleep Problems in Typically Developing Children .....</b>	<b>13</b>
<b>2.3 SLEEP RESEARCH IN CHILDREN WITH FXS.....</b>	<b>14</b>
<b>2.4 SLEEP RESEARCH IN CHILDREN WITH OTHER</b>	
<b>NEURODEVELOPMENTAL DISORDERS .....</b>	<b>15</b>
<b>3.0 METHODS .....</b>	<b>20</b>
<b>3.1 SAMPLE.....</b>	<b>20</b>
<b>3.2 PROCEDURES.....</b>	<b>21</b>
<b>3.3 MEASURES.....</b>	<b>22</b>
<b>4.0 RESULTS .....</b>	<b>26</b>

<b>5.0</b>	<b>DISCUSSION .....</b>	<b>39</b>
<b>5.1</b>	<b>SUMMARY OF RESULTS .....</b>	<b>39</b>
<b>5.1.1</b>	<b>Descriptive Data on Sleep Problems .....</b>	<b>40</b>
<b>5.1.2</b>	<b>Use of Sleep Medication.....</b>	<b>43</b>
<b>5.1.3</b>	<b>Actigraphy .....</b>	<b>44</b>
<b>5.1.4</b>	<b>Caregiver Mood .....</b>	<b>45</b>
<b>5.1.5</b>	<b>Limitations.....</b>	<b>46</b>
<b>5.1.6</b>	<b>Future Investigations .....</b>	<b>47</b>
<b>5.1.7</b>	<b>Conclusions.....</b>	<b>48</b>
	<b>REFERENCES.....</b>	<b>49</b>

## LIST OF TABLES

Table 1 Average Daily Hours of Sleep.....	8
Table 2 Percentage of Children Having Sleep Problems Several Times a Week.....	17
Table 3 Proportion of Prevalent CSHQ Items Across Age Groups.....	29
Table 4 Comparison of Actigraph Parameters.....	32
Table 5 Comparison of Sleep Diary Parameters across Age Groups (N = 95) .....	34
Table 6 Mean (Minimum Score <sup>a</sup> ) of Caregiver Mood per Age Group.....	36

## LIST OF FIGURES

Figure 1 Fragile distal arm of X chromosome .....	4
Figure 2 DNA the molecule of life with typical CGG arrangements .....	4
Figure 3 Distribution of CSHQ Scores .....	28



## **PREFACE**

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## **1.0 INTRODUCTION**

There are several compelling reasons to examine sleep patterns in children with fragile X syndrome (FXS). First, there is a scant body of research examining sleep patterns in children with FXS. Only one descriptive study emerged from an extensive review of the literature, which reported sleep problems in 10 of 13 children with FXS as perceived by their parents (Richdale, 2003). Anecdotally, parents report considerable stress and hardship related to sleep disturbance in the clinical setting. Commonly reported sleep issues for children with FXS include sleep latency greater than 30 minutes, multiple night awakenings, early rising, staying awake all night and wandering around the house, demanding to be in the caregivers' bed, and refusal to sleep alone.

Second, current available literature indicates a higher frequency of sleep related problems in children with cognitive and behavioral delays compared to the typically developing population (Bramble, 1996). While children with FXS clearly have more cognitive and behavioral delays than typically developing children, the nature and extent of sleep-related problems in these children has not been adequately investigated (Richdale, 2003).

Third, sleep problems represent a pressing pragmatic issue in the lives of families of children with FXS because the resulting sleep fragmentation and disruptions have the potential to lead to sleep deprivation for multiple family members caring for these children, creating layers of

potential negative interactions (irritable, sleep-deprived parents interacting with irritable, sleep-deprived children).

Fourth, advances in developmental neuroscience reveal that sleep plays an essential role in learning and memory consolidation, especially during early periods of development, thus optimal sleep is essential to support learning and development. This may be especially important in children with developmental impairments such as FXS.

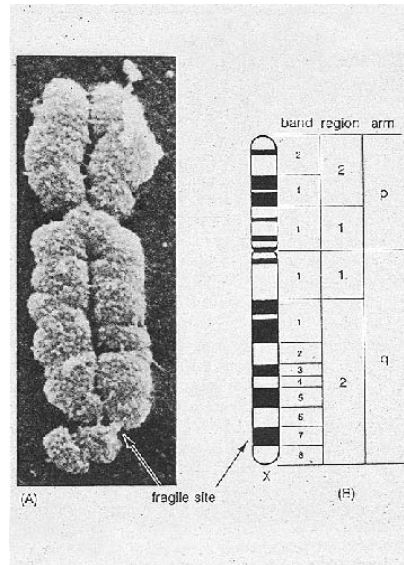
Fifth, information from this study may identify easily applicable and practical interventions.

Finally, adding information to the already existing, but thin, body of research may generate additional research questions that will prompt more extensive empirical studies.

## **2.0 LITERATURE REVIEW**

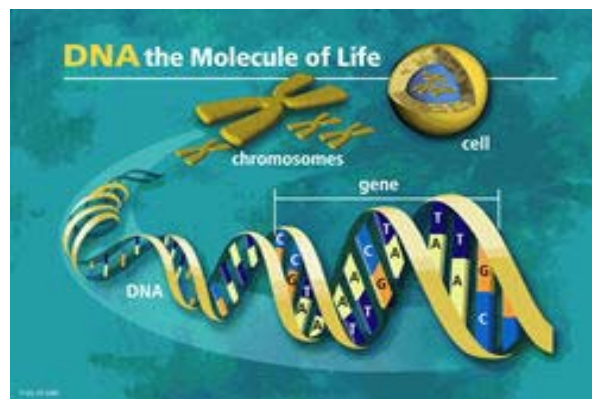
### **2.1 A SYNOPSIS OF FRAGILE X SYNDROME**

Today we recognize over 70 specific forms of mental retardation linked to the X chromosome. FXS is one of the most recognized and is nearly always introduced as the leading inherited, genetic cause of mental retardation. The first description of Fragile X occurred in 1943. Martin and Bell (1943) published an article entitled, “A pedigree of mental defect showing sex – linkage” where they described a family of 11 males with mental retardation and a few less affected females. This syndrome was coined “Fragile” X in the 1970’s when cell culture media deficient in folic acid portrayed the chromosome material in the distal arm of the X chromosome as barely held by the remainder of the chromosome.



**Figure 1 Fragile distal arm of X chromosome**

This visualization method was the diagnostic test for FXS until 1991 when the actual gene was identified on site Xq27.3 (Visootsak, Warren, Anido, & Graham, 2005). The unstable area contained an increased number of CGG trinucleotide repeats and has thus been known as the fragile X mental retardation gene (FMR1). This single alteration is responsible for over 95% of FXS (Sherman, 2002, in Hagerman & Hagerman).



**Figure 2 DNA the molecule of life with typical CGG arrangements**

Presently, there are four forms of the FMR1 gene with respect to length of CGG repeats. In the typical population a normal number of CGG repeats ranges from 6 to 40 repeats, with 30 being the average number. The gray or intermediate zone occurs from 41 to 60 repeats, the

premutation or carrier form is 61 to 200 repeats, and the full mutation occurs at greater than 200 repeats (Visootsak et al., 2005). Hagerman and Hagerman (2002) reported that “there is not yet universal agreement as to the number of repeats that should define the lower limit for the premutation range,” so these parameters can vary by a few repeats (p. 278).

### **2.1.1 Prevalence, Etiology, and Clinical Presentation**

Population based studies suggest the prevalence of the full FXS in Caucasian males ranges from 1:3,717 to 1:8,918 (Crawford, Acuna, & Sherman, 2001; Crawford, et al., 1999; Turner, Webb, Wake, Robinson, 1996). There have been no population-based studies on the full mutation in females but an estimated prevalence of 1:8000 is cited based on transmission rates to offspring (Crawford et al., 2001; Visootsak et al., 2005). Recent population studies have indicated a much higher incidence of the premutation in the general population than previously thought. Several population studies conducted in Canada, Israel, and Italy have revealed a prevalence rate closely approaching 1:100 females in the general population (Hagerman & Hagerman, 2002; Rousseau, Rouillard, Morel, Khandjian, & Morgan, 1995; Toledano-Alhadeff et al., 2001).

The clinical or phenotypic presentation of FXS has broadened over time. Hagerman (2006) calls FXS a “portal disorder” that will help our understanding of other complex genetic conditions, including autism, ADHD, anxiety, mood instability, epilepsy, and neurodegenerative disorders. When a full mutation of greater than 200 CGG repeats occurs, the gene product known as Fragile X Mental Retardation Protein (FMRP) is absent or deficient, causing many of the physical, behavioral, and cognitive characteristics of FXS (Hagerman, 2002; Hart, AAP News, 1998; Loehr, Synhorst, Wolfe, & Hagerman, 1986; Masumeci et al., 1995).

The FMRP level in the premutation allele can be normal or not, therefore it is possible to have FXS and many of its features even as a carrier. In addition, elevated levels of mRNA occur in the premutation causing brain dysfunction, primary ovarian insufficiency (POI), anxiety, social phobia, and depression and has also been associated with such disorders as autism spectrum, ADHD, learning disabilities, and fragile x tremor ataxia syndrome (FXTAS) (Farzin et al., 2006; Goodlin-Jones, Tassone, Gane, & Hagerman, 2004; Hagerman, 2006; Jacquemont et al., 2004; Visootsak et al., 2005).

In regard to cognition, Hagerman (2006) noted that studies with large samples find a significant association between IQ and FMRP level. Typically only 15% of males, but 70% of females, with FXS have an IQ greater than or equal to 70 (Hagerman, 2006). Fisch and colleagues (1996) found that both sexes show a decline in IQ scores and adaptive functioning as they age. Decline occurs in all areas: verbal reasoning, abstract/visual ability, quantitative skills, and short-term memory. Adaptive behavior also declines in all areas: communication, daily living skills, and socialization. This is not due to regression in abilities but more likely reflects a slower rate of acquisition and inability to keep pace with peers (Visootsak et al., 2005).

Hatton and colleagues (2003) found that boys with FXS who demonstrate less autistic behaviors and who have a higher level of FMRP demonstrated better performance in all adaptive areas than those with more severe autism. Hatton, Bailey, Hargett-Beck, Skinner, and Clark (1999) studied the behavioral style of 45 boys with the full mutation of FX and reported that boys with FXS were significantly more active and less approachable, adaptable, intense, and persistent compared to a sample of typically developing children. Only 16 FXS boys were categorized as easy, difficult, or slow to warm up, indicating that these traditional categories “do not adequately describe the temperament of boys with FXS” (p. 630). Intellectual disability was

found to be separate and distinct from temperament reports since severity of disability was not significantly linked to temperament score. Also temperament scores remained stable over time.

## **2.2 SLEEP PATTERNS IN TYPICALLY DEVELOPING CHILDREN**

### **2.2.1 A Brief Tour of Sleep Architecture**

Sleep can be divided into two main categories, non-rapid (NREM) and rapid (REM) eye movement phases. Furthermore, NREM can be divided into the following four stages (percent of main sleep period): Stage 1 (4-5%); Stage 2 (45-55%), Stage 3 (4-6%), and stage 4 (12-15%). Stages 3 and 4 NREM are the deepest levels of sleep and often referred to as “slow wave sleep” (SWS) or “delta sleep”. They are more prominent in younger children. In infancy REM sleep is as high as 50% and infants enter this level at the start of sleep, suggesting a significant role of REM sleep in brain maturation. Developmentally, sleep has a “central role in early maturational processes” and may be considered the primary activity of the brain in a child’s early years (Dahl, 1996, p. 3). Starting around 24 months, REM decreases to 20-25% per night and where most dreaming and a high level of brain metabolism occur, contrasted by skeletal muscle paralysis. (Stores, 2001, in Stores and Wiggs). Alternating cycles of NREM and REM sleep occur throughout the night.

Several biological and environmental factors influence our circadian or sleep-wake rhythm. The hypothalamus mainly controls the timing of sleep as well as our body temperature and cortisol production. For the most part, by 12 months of age, healthy children have shifted to sleeping at night and wakefulness during the day. Stores (2001) reported that this shift is



influenced by both light perception and social cues such as “mealtimes and social activities, ambient temperature and noise levels, and internal body signals such as hunger and temperature” (p.12). The hormone melatonin is suppressed by exposure to bright light and is mainly produced by the pineal gland during darkness. The production of melatonin influences circadian rhythms via a biologic feedback system between the pineal gland and hypothalamus. Developmentally, night-time levels of melatonin peak between the ages of one and three years, then a decline begins, which is most apparent at the onset of puberty. Several other biological changes are also associated with pubescence including less SWS and delay in the timing of this sleep phase, and a decline in amount of sleep required. Usually from age five years, and up until puberty, most children are quite alert during the day. The amount of sleep duration varies with chronological age as seen in Table 1.

**Table 1 Average Daily Hours of Sleep**

Term Birth	16 – 18
1 year	15
2 years	13 – 14
4 years	12
10 years	8 – 10
Mid-adolescence	8.5
Late adolescence	7 – 8

(Source: Adapted from Stores and Wiggs, 2001)

### 2.2.2 Classification of Sleep Disorders

For children with sleep disorders there appears to be no appropriate classification system. The American Psychiatric Association defines many sleep disorders based on adult criteria and few children meet that level of impairment to make an appropriate diagnosis. Gaylor, Goodlin-Jones, and Anders (2001) further elaborated on this deficiency by referring to *The International Classification of Sleep Disorders: Diagnostic and Coding Manual* (ICSD – DCM) and pointing out that “the labels are cumbersome and the criteria are neither empirically nor developmentally determined” (p. 61). Their review of another classification scheme developed by Zero to Three (DC 0-3), which focuses on young children within this age group, concluded that this scheme did not provide “empirically derived, quantitative metrics ... to aid in the classification of sleep problems” (pp. 61-62). Stores and Wiggs (2001) also recognized that the ICSD is adult oriented and needs modifications for the pediatric population. Gaylor and colleagues (2001) posited that “an age appropriate and culturally sensitive classification scheme that can be used reliably by researchers and clinicians alike” needs to be developed (p.62).

One nosology not mentioned in the research on sleep in children is the *International Classification of Functioning – Children’s Version (ICF-CY)* (WHO, 2005). The World Health Organization (WHO) created the International Classification of Functioning, Disability, and Health (ICF) to describe the bidirectional effects of health conditions on body functions and structures, daily activities, and social participation for all ages. The ICF was developed to assure a common language across disciplines, cultures, age groups, and disabilities. The ICF-CY version can serve as an appropriate theoretical framework to define and categorize sleep functions in children. Sleep functions are defined as “generic mental functions of periodic, reversible and selective physical and mental disengagement from one’s immediate environment

accompanied by characteristic physiologic changes” (WHO, 2005). They are listed under the broad category of Body Functions and more specifically contained in the domain of Mental Functions. Subcategories of sleep functions are listed as:

*Amount of sleep:* mental functions involved in the time of sleep spent in the state of sleep in the diurnal or circadian rhythm.

*Onset of sleep:* mental functions that produce the transition between wakefulness and sleep.

*Maintenance of sleep:* mental functions that sustain the state of being asleep.

*Quality of sleep:* mental functions that produce the natural sleep leading to optimal physical and mental rest and relaxation

*Functions involving the sleep cycle:* mental functions that produce REM sleep and NREM sleep.

As this paper explores sleep patterns in children with Fragile X syndrome and compares and contrasts that population to typically developing children and those with other neurodevelopmental disabilities, many of the sleep problems will fall into the subcategories of sleep functions defined by WHO. For example, parasomnias, a term familiar to few families and limited professionals, are defined as disturbances that alter the sleep process- such as sleep walking, confusional arousals, sleep terrors, teeth grinding and night-time bed wetting to name a few. When using the ICF, these are considered conditions that interrupt the quality of sleep and the sleep cycle. Dyssomnias cause difficulty getting to sleep, staying asleep, and causing excessive sleepiness during the day. They can be due to intrinsic, extrinsic, or circadian rhythm factors. For example, obstructive sleep apnea (OSA) is an intrinsic factor; external factors may cause a reluctance to go to bed or early sleep awakenings; and circadian rhythm disorders may cause an advanced or delayed sleep onset. Most of these behaviors involve the ICF subcategories of amount or onset of sleep.

Stores and Wiggs (2001) underscore four ways that disorders of sleep in children differ from adults:

- Parenting factors can be an extrinsic influence in the cause of childhood sleep disorders.
- Sleep problems can have a wide ranging influence on intellectual and behavioral development.
- Over-activity and other forms of disturbed behavior, such as attention deficit hyperactivity disorder (ADHD), result from sleep disorders in children, whereas adults tend to be sleepy and under-active.
- Childhood sleep disorders are very treatable.

### **2.2.3 Typical Assessment of Sleep Disorders**

Ferber (1996) recognized that “the complaint of pediatric sleep disturbance almost always comes from the parent or caretaker” (p. 569). However, Gaylor and colleagues (2001) identified what they called “an unresolved controversy” and asked, “Should parental distress about a child’s sleep be the primary criterion for diagnosis?” (p. 62). One particular study (Hering, Epstein, Elroy, Iancu, & Zelnik, 1999) identified parents of children with autism as over-reporters and attributed this to their “oversensitivity” to sleep issues; however, the majority of studies on sleep disturbances either in the typical or special needs population identified parents as accurate or under-reporters.

Collecting information from a variety of sources can help validate the presence of a sleep disorder. A sleep history obtained from parents and child should include many factors, such as the exact nature of the disturbance, triggers, and effectiveness of previous treatments. Ferber (1996) stressed that “bedtime routines are important to clarify and it should be learned what happens all the way through the act of falling asleep” (p.571). Stores and Wiggs (2001) advised

documenting a 24-hour sleep–wake schedule; supplemented by a brief, general questionnaire (e.g., *The Epworth Sleepiness Scale*). A more revealing approach compared to retrospective data gathering is a 2-week sleep diary that can identify wake time, number and length of naps, time to bed, time to sleep, and time and length of awakenings.

Objective data can be collected by audio-visual recording, actigraphy, and polysomnography. Anders, Halpern, and Hua (1992) incorporated time lapsed video recording in the home of infants at the age of 3 weeks and 3 months. The time lapse allowed 12 hours of sleep to be played back in one hour. These authors were able to reliably score active sleep, quiet sleep, and wake periods. In addition, out-of-crib time, parent-child interaction, and parental interventions during the night could be coded from this technique.

A more practical option to use in the home environment is actigraphy. An actigraph is a watch-like movement detector that is placed on a child's wrist or leg and registers movement for prolonged periods. This device does not record sleep staging, however it is a reliable method of data collection for sleep-wake patterns including timing, continuity, and duration of sleep. Sadeh, Lavie, Scher, Tirosh, and Epstein (1991) reported agreement rates of actigraphy with polysomnographic recording (PSG) to be between 80-90% for both children and adults. Detailed information on sleep stages can best be obtained by PSG, which involves an electroencephalogram (EEG), electrooculogram (EOG), and electromyogram (EMG). Stores and Wiggs (2001) identified three main indications to implement a PSG: daytime sleepiness, complicated parasomnias, or objective data collection of a sleep complaint or response to treatment.

#### **2.2.4 Prevalence of Sleep Problems in Typically Developing Children**

Severity and prevalence of sleep problems in typically developing infants and children are generally viewed as developmentally based and primarily involve issues of settling and night awakenings. Studies on typically developing children, ages 1 to 4 years old, report a range of sleep difficulties between 10 to 40% (Armstrong, Quinn, & Dadds, 1994; Bramble, 1996; Johnson, 1991; Kataria, Swanson, & Trevathan, 1987; Sadeh, Lavie, Scher, Tirosh, & Epstein, 1991; Zuckerman, Stevenson, & Bailey, 1987). Johnson (1991) divided her sample into night wakers and sleepers, observing that the “infants and toddlers who were nursed, rocked, or comforted to sleep were more likely to be night wakers” and that 80% of infants and two thirds of the toddlers who slept through the night did not receive such interventions prior to sleep and were considered “self-soothers” (p. 110). Her findings underscore a possible association between bedtime routine and sleep patterns, a hypothesis considered in the present study. Quine (2001) stated that sleep problems persisting at age three become chronic for two thirds of children. A parent survey of children aged 5-12 years revealed that 27% exhibited bedtime resistance, 11% had sleep-onset delays, 7% night awakenings, 17% morning wake-up problems, and 17% complained of fatigue (Blader, Koplewicz, Abikoff, & Foley, 1997). Owens, Spirito, McGuinn, and Nobile (2000) identified 37% of children in their sample of elementary school-aged children as having at least 1 significant sleep problem. Sadeh, Gruber, and Raviv (2002) reported that older children, grades 2, 4, and 6, with poor sleep (averaging at least three awakenings per night and 10% of the night was in wakefulness after sleep onset) had significantly higher scores on the *Child Behavior Checklist* (CBCL) compared to good sleepers. Their findings suggest either that generally dysregulated children also have poorer sleep, or typically developing children with poor sleep are at risk for compromised neurobehavioral

functioning (NBF). Since the latter is already compromised in children with FXS, studying sleep patterns in children with FXS is all the more critical so as to optimize their functional level.

### **2.3 SLEEP RESEARCH IN CHILDREN WITH FXS**

Hagerman, Riddle, Roberts, Breese and Fulton (1995) surveyed parents of 35 patients with FXS who were prescribed clonidine and found that 37% of the children received clonidine to treat sleep issues and 54% of the parents were satisfied with its use for this purpose. Gould and colleagues (2000) investigated a possible association between melatonin levels, sleep patterns, and hyperactivity. This study revealed significantly greater variability in total sleep time, mean sleep onset latency, number of night-wake episodes, and variability in sleep termination times all higher in the FXS group. The CBCL scores on the *Attention Problems Scale* were significantly higher for the FXS males. Interestingly, the mean melatonin level was higher for the boys with FXS at all time points. The fact that the FXS subjects had both increased melatonin levels and significant sleep problems was quite unexpected because difficult sleep behaviors normally imply lower levels of melatonin. Musumeci and colleagues (1995) investigated the neurophysiology of sleep in FXS. The FXS subjects had significantly less total and REM sleep times, an increase in the first REM latency and slow wave sleep, and they experienced a significant increase in twitch movements during REM. These investigators concluded that their findings are similar to those found for other children with cognitive delay and suggested that a possible dysregulation in certain neurochemical mechanisms controlled by the brainstem may explain these results.

Richdale (2003) stated, “The nature of sleep problems in children with FraX, as perceived by their parents, has not been reported, but the limited available literature suggests that sleep problems are an issue” (p.136). Richdale reported on 13 children with FXS and noted that 10 of the children (77%) demonstrated current or previous problematic sleep behaviors. Parent reporting of a current sleep problem was positively associated with level of child psychopathology and with parental stress. Richdale concluded that “the perceived stressfulness of sleep difficulties, general parental stress and child behavior problems appear to influence the parents’ perceptions of their child’s sleep difficulties rather than either duration or frequency of these problems” (p. 141). She also stated that “long-standing sleep problems may be more tolerable if they are not perceived as severe or stressful and if the child has less problematic behavior.” Therefore she advised clinicians to be aware of the existence of sleep problems even when parents fail to report them (p.142). Additional studies are required to investigate the links between sleep and behavior difficulties, stress, and parents’ perceptions of sleep problems. The proposed investigation will examine associations among parent perception of sleep difficulties, parent mood, and bedtime routine.

## **2.4 SLEEP RESEARCH IN CHILDREN WITH OTHER NEURODEVELOPMENTAL DISORDERS**

In 1996, Johnson reviewed the research on sleep problems in children with mental retardation (MR) and/or autism and discovered “a striking paucity of studies systematically examining sleep problems” in this particular population even with a prevalence rate of sleep disorders ranging between 34%-80% in children with mental retardation (p.674). She added, “Despite the dearth



of investigative efforts, there are numerous, compelling reasons to hypothesize that children with mental retardation and autistic disorder are at particular risk for sleep problems” (p.675). These compelling reasons include medical conditions, behavior problems, and parental distress of parenting a child with special needs. Similar medical conditions and behavior problems are associated with FXS.

In their investigation, Schreck and Mulick (2000) compared five groups of children, including autism (n = 38), PDD (n = 17), MR (n = 22), typically developing (n = 43) and special education (n = 49). Children with autism and PDD were eventually pooled into one group (autism). These researchers did not find any significant differences among all groups in the total hours of sleep at night, hours slept in the last 24 hours, or number of naps taken per day as a function of age or group. However, the autism group scored significantly higher than other groups on nightmare type of disturbances and environmental disturbances (i.e., fear of noises, sleeping places other than own room). Cessation of breathing, teeth grinding, and the use of sleep aids such as medications or pacifiers were both significantly higher for autism group relative to the typically developing and special education groups, but not for children with MR. The autism group also scored significantly higher than the MR group on problems associated with disorientation upon awakening. This study was unique in that it provided a missing link in the literature on sleep disorders in children with developmental disabilities by specifically describing dyssomnias and parasomnias in this population.

One of the most compelling and frequently referenced studies in the area of sleep research and children with developmental disabilities was conducted by Quine in 2001. Children in special schools exhibited a higher proportion of sleep problems. These significant differences have been condensed and summarized in Table 2. All four dyssomnias reduced with age in the

mainstream group. In the special school group, only two dyssomnias were age related, sleeping in the parents' bed and waking at night. Therefore, settling problems and early waking in children with cognitive delays are less likely to be outgrown and may require some form of intervention in order to prevent a chronic sleep problem. Data collected on the pattern of dyssomnias, parasomnias, and OSA features in children with FXS in the present study can be compared to these findings.

**Table 2 Percentage of Children Having Sleep Problems Several Times a Week**

	<b>Mainstream (n = 576) % n</b>	<b>Special School (n = 182) % n</b>	<b>Chi Square</b>
<b>Dyssomnias</b>			
Settling problems	27 (127)	41 (74)	12.1**
Night waking	13 (76)	45 (82)	85.1**
Parents' bed	11 (62)	17 (31)	5*
Early waking (< 5AM)	5 (26)	14 (24)	43.8 **
<b>OSA features</b>			
Restlessness	26 (151)	53 (96)	44.3**
Loud snoring	14 (83)	27 (49)	15.1**
Apneic episodes	1 (6)	3 (6)	4.5*
Gags/chokes	1 (6)	3(6)	4.5*
Daytime sleepiness	3 (17)	13 (24)	28.3**
<b>Parasomnias</b>			
Headbanging	2 (10)	4 (8)	4.2*
Bedwetting	5 (28)	33 (60)	106.5**

\*\*  $P < 0.001$ ; \*  $P < 0.05$

Adapted with permission from the author, "Sleep problems in primary school children: Comparison between mainstream and special school children," by L.Quine, 2001, *Child: Care, Health and Development*, 27(3), p. 209.

Richdale, Francis, Gavidia-Payne, and Cotton (2000) investigated not only sleep problems in children with intellectual disability (ID) but also the role sleep problems may play as environmental stressors on parents. The authors discovered that the children with ID had

significantly higher frequencies of both past and current sleep problems, more frequent night awakenings, and yelling at night than the comparison group. A bedtime routine was in place for the vast majority in the comparison (90.2%) and ID (80%) groups. Settling difficulties, night waking, and restless sleep were associated with significantly higher levels of stress in parents of the ID group. *Parenting Hassle* scores were more than doubled for the ID group. In addition, families within the ID group that reported sleep problems also reported a significantly greater frequency and intensity of hassles than those in the ID group without sleep problems. The ID group was further delineated into three levels of disorder severity - mild, moderate, and severe/profound - to determine any additional associations with sleep problems. Descriptive analysis showed past sleep problems to occur at 50%, 70.8%, and 73.3% and current sleep problems occurred at 50%, 52%, and 73.3, respectively, with progressive levels of impairment. Richdale and colleagues recommended further investigation into the complex associations of sleep, behavior problems, and parental stress and emphasized the need to develop specific supports for parents and children with disabilities “to strengthen their psychological well-being” (p.159).

Honomichl, Goodlin-Jones, Burnham, Gaylor, and Anders (2002) examined parent report of stress and sleep wake patterns in 100 children with pervasive developmental disorder (PDD). These authors found the initial report of sleep problems (54%) comparable to other studies of children with PDD. Unique to this study was the discovery that regardless of age and parental report, all children demonstrated an extended time to fall asleep and awakened more often and for longer periods compared to studies of typically developing children. Average *Child's Sleep Habits Questionnaire* (CSHQ) subscale scores of children with PDD neared the clinical range of children typically referred to a sleep clinic; however 46% of those parents did not report an

initial sleep problem. The authors proposed that regulating bedtime routine may assist in the organization of sleep onset. Parenting report of sleep problems and the implementation of bedtime routine will be further investigated in the present study with the addition of actigraphy data collection, areas endorsed by Honomichl and colleagues as needing further investigation in children with developmental disabilities.

In the present study, the following hypotheses will be tested:

1. Children with FXS will exhibit problematic sleep patterns.
2. Problematic sleep patterns will be positively associated with caregiver's negative mood.
3. Regular bedtime routine will be positively associated with lower levels of problematic sleep patterns.
4. Exploratory: Children with FXS who have a greater number of CGG repeats will have more sleep problems. They will also demonstrate a more problematic response to parent negative mood and changes in their bedtime routines.

### **3.0 METHODS**

The study was cross sectional in design with a focus on sleep/wake schedules and sleep patterns in home settings, as well as parent mood, for a sample of youth with FXS.

#### **3.1 SAMPLE**

Children ages 3 years, 0 months to 17 years, 11 months (MA = 7.8 years) with either a full, premutation, or intermediate allele size of FXS were included in this study. Those families recruited through the Fragile X Center Registry at Children's Hospital of Pittsburgh were contacted by phone and offered the opportunity to participate in a study examining sleep patterns in children with FXS. At the 10th International Fragile X Conference in Atlanta, a poster using the same phrasing as the phone script to describe the study was displayed on a Children's Hospital of Pittsburgh informational table. Attendees to the conference were then able to initiate their interest to participate. 126 children were enrolled in the study; 95 children (75%) completed the study representing 81 families. Ninety-five percent of the sample resided within the contiguous United States. The remaining 5% resided in Canada (3); Southeast Asia (1); and Switzerland (1). 15% were patients who had been evaluated at the local Fragile X Center at the Children's Hospital of Pittsburgh.

Study participants were 95 children with FXS, 74 children with a full mutation (allele range >200 to 1600); 16 participants with mosaicism; three children with a premutation (allele sizes of 68, 70, and 90); and two children with intermediate alleles of 47 and 49. Seventy-six (80%) participants were male. There were 14 sibling pairs. Respondent caregivers included mothers (97%), grandmothers (2%) and one father (1%). Eighty-seven per cent were married; 13% were single, divorced, or widowed. The mean age of the respondent caregiver was 39 years; range was 29 to 55 years. Ethnic background of caregiver included White (91%), African American (4%), Hispanic (3%), Asian (1%) and Native American (1%). Half of the caregivers had four year college degrees; an additional 22% received a graduate degree or higher; 12% had post-high school training or associate degrees; 6% reported high school and 11% reported elementary school as the highest level of education completed. Fifty-one per cent of respondents earned incomes greater than \$75, 000; 20% earned \$50 to \$75, 000; 22% earned \$30 to \$50, 000 and six percent earned less than \$30, 000. Number of household members ranged from 2-7, with a mean of 4 members (59%). The families resided in the suburbs (72%), rural areas (19%) or urban (9%) settings.

## **3.2 PROCEDURES**

Families who provided their contact information in Atlanta at the 10<sup>th</sup> International Fragile X Conference were contacted by phone and additional information explaining the study was provided. Families in Europe and Southeast Asia were contacted by e-mail. The families that initiated interest via FXS list serves electronically provided their contact information so a consent form could then be mailed to their home. Upon return of the signed consent, a sleep

assessment packet was sent to the home. This packet included the measures described below and a self-addressed, stamped return envelope. An actigraph was included in the package sent to the local group of families. Upon completion of the study families received a monetary reimbursement.

### 3.3 MEASURES

Parents were asked to complete three questionnaires including a Background Information Sheet; a Bedtime Routine Information Sheet; and the *Child's Sleep Habits Questionnaire, Preschool and School-Aged, Abbreviated Version* (CSHQ). The sleep packet also contained a 14-day sleep diary, requiring a brief entry each morning and night. All forms were completed by a caregiver in the home. In addition, children in the local group were asked to wear an actigraph for seven consecutive nights and an additional parent questionnaire, the *Positive and Negative Affect Schedule* (PANAS), was added to their protocol.

The *Background Information Sheet* consists of questions regarding demographics, information on the caregiver including educational background, current work, ethnic background, and allele status of child with FXS.

The *Bedtime Routine Information Sheet* was specifically developed for this research to ascertain whether the child has a typical bedtime routine and, if so, the order of routine evening activities. In an open ended format, parents were also asked what they thought was the greatest challenge in starting or keeping a bedtime routine. If no routine was specified, the parent was asked if his/her preference would be to have a routine in place.

*The Child's Sleep Habits Questionnaire, Preschool and School-Aged, Abbreviated Version* (CSHQ; Owens, Spirito, & McGuinn, 2000) includes 33 questions about sleep disturbances. Test-retest reliability over a three-week period for both normal and sleep-referred clinical populations has been established at a satisfactory level ( $r$ 's = .62-.79). Items on this scale are rated on a 3-point Likert scale: 0-1 night per week = rarely; 2-4 nights per week = sometimes; 5-7 nights per week = usually. Sample items include: "Child goes to bed at the same time every night;" "Child is afraid of sleeping in the dark;" "Child wets bed at night;" and "Child seems tired." A total of eight subscales are included: Bedtime Resistance, Sleep Onset Delay, Sleep Duration, Sleep Anxiety, Night Waking, Parasomnias, Sleep Disordered Breathing, and Daytime Sleepiness. Higher scores indicate more disturbed sleep. A cut-off score of 41 yields the best diagnostic confidence for identifying clinically significant sleep problems with a sensitivity of 0.80 and specificity of 0.72 (Owens et al., 2000).

*Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988)* is a brief scale to measure dimensions of mood. The assessment consists of ten positive affects (PA) (e.g., interested, excited, strong,) and ten negative affects (NA) (e.g., distressed, upset, guilty). Participants rate the extent to which they have felt the different feelings during the past week on a scale from 1 to 5, where 1 = "very slightly or not at all" and 5 = "extremely." Total positive or negative affect scores range from 10 – 50. Watson et al. (1988) showed the mean NA score to be 18.1 (SD = 5.9) and the mean PA score as 35 (SD = 6.4) in their normative group.

Coefficient  $\alpha$ 's are adequate, averaging .88 for PA and .86 for NA, and are unaffected by time parameters. Between scales correlation is -.09. All 20 descriptors have primary loadings of .50 or above on the appropriate factor with low secondary loadings.



A *Sleep Diary* was developed for this work based on current research questions and after investigating previous diaries utilized in sleep research (Honomichl, 2002). Diary entries were completed for 14 days. Each morning caregivers were asked to record the following items on the child's previous night's sleep: (1) time of entry to bed and whether it was regular, earlier, or later than normal for this child; (2) whether sleep latency was greater than 30 minutes; (3) whether child fell asleep in own bed; (4) number of night awakenings from sleep; (5) whether child moved to someone else's bed; (6) morning awake time and whether that was regular, earlier, or later than usual; and (7) whether child had difficulty waking for the day.

Each evening the caregiver recorded the number of naps during the day; whether medication was used to induce sleep and, if so, the name and dosage; and if the bedtime routine that occurred that evening was normal for that child.

*Parent Mood Assessment.* As part of the evening portion of the sleep diary one or two caregivers recorded how they felt prior to their child's bedtime. A scale provided a 10-point range contrasting three sets of emotions (sad/happy, angry/pleasant, and overwhelmed/relaxed). The caregiver circled the number on each range that best described his/her level of emotion. Higher scores indicate a more positive mood. Reported internal consistency of the 3 sets of emotion ratings ranges from .78 to .89 (Quittner et al., 1998).

*Actigraphy.* This was performed on the local clinic sample only. Actigraphs allow quantification of sleep patterns in the natural home environment. The actigraph used was the Motionlogger Octagonal Basic. It is feasible that wearing the actigraph may cause initial disturbance in sleep, underscoring the need to collect 5-7 days of recordings. Data were analyzed on the following parameters:

**Length of time in bed:** minutes from start to end of sleep recording interval.

**Activity Mean** (Amean): mean activity score recorded as counts per epoch. An epoch is set at 60 second intervals.

**Activity Median** (Amed): Median activity score (counts/epoch)

**SD of activity mean** (Asd): Standard deviation of the activity mean

**Wake Minutes** (Wmin): total minutes scored as wake

**Sleep Minutes** (Smin): total minutes scored as sleep (sleep + light sleep)

**% Sleep** (Pslp): percent minutes scored as sleep ( $100 * (\text{sleep} + \text{light sleep}) / \text{duration}$ )

**Sleep efficiency** (Seff): number of minutes of sleep divided by 0-0 interval (down time minus sleep latency or terminal wake episode) times 100.

**Sleep Latency** (Slat): minutes to start of first 20-minute block with > 19 min sleep.

**Wake after sleep onset** ((Waso): wake minutes during 0-0 interval.

**Activity Index** (Actx): percent epochs with > 0 activity score

**Wake Episodes** (Wep): number of blocks of contiguous wake epochs

**Mean Wake Episode** (Mwep): mean duration of wake episode in minutes

**Longest Wake Episode** (Lgwep): duration of longest wake episode in minutes

**Sleep Episodes** (Sep): number of blocks of contiguous sleep epochs

**Mean Sleep episode** (Msep): mean duration of sleep episode in minutes

**Longest Sleep Episode** (Lgsep): duration of longest sleep episode in minutes

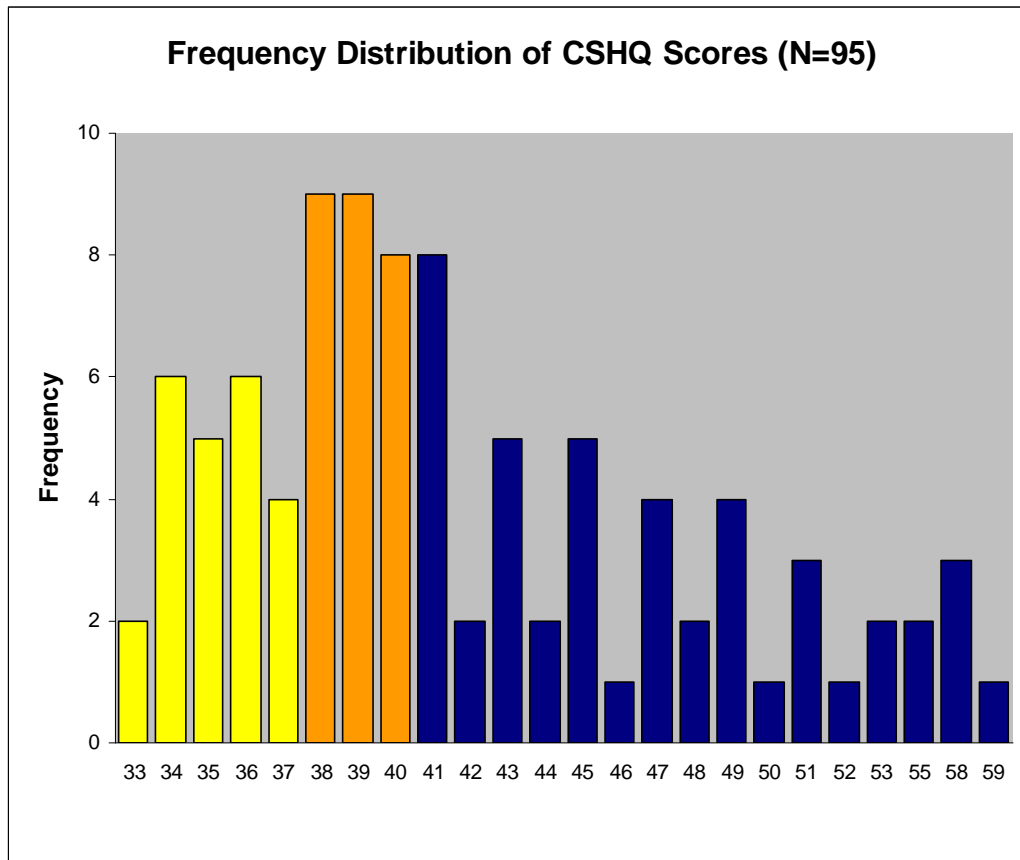
## 4.0 RESULTS

To test Hypothesis 1, that children with FXS will exhibit many problematic sleep patterns, descriptive statistics were computed on data obtained from parent questionnaires (*Bedtime Routine Sheet*, *CSHQ*, *PANAS*), actigraphy, and sleep diaries. Information was aggregated to obtain frequencies for categorical data, as well as means, standard deviations, medians, and ranges for continuous data. Mann-Whitney, Kruskal-Wallis, Pearson Chi-square tests were conducted based on age, gender, and various family factors. Sample size ( $N = 95$ ) was sufficient to detect a medium effect size ( $r = .3$ ) with a power of .8 (Cohen, 1992). Raw actigraphy data were first transformed into sleep variables using the ACTme Software and Analysis package from Ambulatory Monitoring, Inc. Mann-Whitney tests were conducted on pilot actigraphy data comparing a small sample of children with FXS ( $n = 7$ ), to a group of low risk typically developing controls ( $n = 14$ ) matched by age.

The *Bedtime Routine Information Sheet* revealed that all respondents ( $N = 95$ ) reported that the target child had a consistent evening routine. Bedtime ranged from 7:00 PM (4%) to 10:00 PM (2%); with a mode of 8:30 PM (25%). The number of activities included in the evening routine ranged from 2 – 10. The mode and mean were 5 activities. Activities reported as part of the evening routine included: dinner (96%), bathing (85%), TV (73%), reading (59%), snack (54%), play with toys (54%), “other” activity including computer (25%), music (22%), visits (14%) and homework (10%). Respondents ( $n = 83$ ) identified the single greatest challenge

to maintaining the bedtime routine as: no challenge (34%), homework (28%), siblings (12%), caregiver tired (11%), work schedule (10%), or child resistance to routine (6%).

The *Child's Sleep Habits Questionnaire (CSHQ)* indicated that morning awakening times ( $n = 92$ ) ranged from 5:00 AM (4%) to 8:25 AM (1%), with a mode of 6:00 AM (24%) and median of 6:30 AM (23%). Usual amount of sleep each day ( $n = 88$ ), combining naps and nighttime sleep, ranged from 7 - 13.5 hours with a mode and median of 10 hours (27%). Maximum amount of minutes awake per night ( $N = 95$ ) ranged from 0 (41%) to 240 (1%), with a median of 5 minutes (15%) and a mean of 22 minutes ( $SD = 45.7$ ). The *CSHQ* ( $N = 95$ ) had a mean total score of 42, with a range from 33 to 59 ( $SD = 6.4$ ). The distribution is diagrammed in Figure 3. A cut-off score of 41 on the CSHQ has the best diagnostic confidence with a sensitivity of 0.80 and specificity of 0.72 (Owens et al., 2000). A sleep score of 41 or greater was reported by caregiver in 48% of the children (shown by dark blue bars in Figure 3); this level of scoring may be worthy of a referral to a sleep clinic. Another 28% of children were clustered between scores of 38-40 (shown by orange bars in Figure 3).



**Figure 3 Distribution of CSHQ Scores**

Undesired items scored as “sometimes” or “usually” or desirable items scored “rarely” were considered prevalent if they occurred 20% of the time or more. A total of 21 prevalent items were identified and are listed in Table 3, which displays percent of occurrence for each behavior per age group. A Pearson Chi-Square compared the proportion of prevalent items across age groups. The 6 items found to be significant appear to follow a typical developmental pattern. For example, as children age, night time bedwetting and sleeping in the car subsides. Surprisingly, most prevalent items did not, in fact, follow a typical developmental pattern and age (group) was not a significant factor. A few of these age-invariant behaviors include: night time awakenings, moving during the night, talking in sleep, restlessness, snoring, and daytime sleepiness.

**Table 3 Proportion of Prevalent CSHQ Items Across Age Groups**

<i>CSHQ</i> Subscale (item #)	Ages 3-17 N = 95	Ages 3-6 n = 41	Ages 7-11 n = 39	Ages 12-17 n = 15	Sig. age difference*
<b>Bedtime Resistance</b>					
Needs parent in room to sleep (5)	21%	17%	31%	7%	
<b>Sleep Onset Delay</b>					
Does not Fall asleep in 20 minutes (2)	42%	51%	33%	40%	
<b>Sleep Duration</b>					
Sleeps too little (9)	33%	49%	21%	20%	.014
Does not sleep the right amount (10)	24%	32%	21%	13%	
<b>Sleep Anxiety</b>					
Needs parent in room to sleep (5)	21%	17%	31%	7%	
Afraid of sleeping in the dark (7)	22%	17%	28%	20%	
Trouble sleeping away (21)	51%	56%	49%	40%	
<b>Night Wakings</b>					
Moves to others bed at night (16)	21%	22%	26%	7%	
Awakes once during the night (24)	51%	56%	51%	33%	
Awakes more than once (25)	26%	24%	31%	20%	
<b>Parasomnias</b>					
Wets the bed at night (12)	38%	49%	39%	7%	.015
Talks during sleep (13)	21%	20%	18%	33%	
Restless and moves a lot (14)	58%	63%	59%	40%	
Grinds teeth during sleep (17)	33%	42%	36%	0%	.012
Alarmed by scary dream (23)	20%	22%	23%	7%	
<b>Sleep Disordered Breathing</b>					
Snores loudly (18)	34%	37%	28%	40%	
<b>Daytime Sleepiness</b>					
Does not wake by him/herself (26)	28%	12%	31%	68%	.000
Wakes up in negative mood (27)	21%	29%	18%	7%	
Others wake child (28)	42%	37%	36%	73%	.031
Hard time getting out of bed (29)	20%	22%	19%	20%	
Seems tired (31)	35%	34%	39%	27%	
Sleeps riding in car (33)	39%	56%	23%	33%	.008

\* Pearson Chi-Square,  $p < .05$

A two-tailed Spearman Correlation ( $N = 95$ ,  $\alpha$  at .05) was not significant for age and total *CSHQ* score. No significant group differences on the *CSHQ* were identified based on child's gender, age group (3-6 years, 7-11 years, 12-17 years), medication (taking medications, not

taking medications for sleep). There were no significant associations on any family demographic variables (i.e., family income, caregiver education, number in household) with total *CSHQ* score ( $n = 81$ ).

Twelve *PANAS* assessments were completed by 11 caregivers. The descriptive data excluded one randomly chosen assessment from a dyadic pair of siblings in order to avoid additive effect on the responses. Ten caregivers had higher Positive Affect (PA) scores than Negative Affect (NA) scores. The mean PA score was 37.5 ( $SD = 6.9$ ) with a range of 24 to 49 compared to a mean NA score of 20 ( $SD = 9.3$ ) with a range of 10 to 35. Both affect means were higher than the reported normative means of Watson and colleagues ((1988) (Mean PA = 35 ( $SD = 6.4$ ); Mean NA 18.1 ( $SD = 5.9$ )), and showed greater variability, particularly in the NA scores.

Sixteen families agreed to participate in the actigraph component of the study. Six children refused to wear the actigraph; data were unobtainable on 2 actigraphs (technical problems); and 1 actigraph was not returned. Usable actigraphy data were available from 7 children. One subject wore the device for four nights, four subjects provided data for five nights, and two provided data for seven nights. Age range of participants with FXS who participated in collection of actigraphy data was 5 to 16 years ( $MA = 8.4$  years). A comparison group matched on age ( $MA 9.6$  years; range 7- 15 years) was selected from a low risk normal control group enrolled at the Western Psychiatric Institute and Clinic Child and Adolescent Sleep Lab. Table 4 shows that children with FXS had a significantly longer time in bed; higher mean, median, and  $SD$  of activity level; more total wake minutes; longer sleep latency; greater number of minutes awake after sleep onset; greater number of contiguous wake episodes; greater duration of longest wake episode; and greater number of contiguous sleep episodes. The FXS group also had a significantly lower percentage of sleep minutes; lower sleep efficiency; and lower mean duration

of sleep episode. All significant findings represented medium sized effects with a range from .46 to .55. There were no significant differences between groups on total minutes scored as sleep; activity index; mean duration of wake episode; and duration of longest sleep episode.



**Table 4 Comparison of Actigraph Parameters**

<b>Sleep Parameter</b>	<b>FX (n = 7) Median (25<sup>th</sup>, 75<sup>th</sup>)</b>	<b>Control (n = 14) Median (25<sup>th</sup>, 75<sup>th</sup>)</b>	<b>Sig. Level</b>	<b>Effect Size</b>
# Minutes in bed	626 (602, 640)	566 (527, 581)	.016*	.52
Mean activity level	32 (19, 36)	16 (13, 22)	.012*	.54
<i>(Counts per epoch (60 sec))</i>				
Median activity score	6 (1, 7)	0 (0, 1)	.014*	.53
<i>(Counts/epoch)</i>				
SD of activity mean	57 (47, 60)	39 (33, 46)	.012*	.54
Wake minutes	149 (65, 162)	48 (35, 77)	.010**	.55
Sleep minutes	469 (432, 586)	490 (460, 557)	.636	.11
Percent sleep (min)	75 (69, 90)	91 (87, 94)	.020*	.51
Sleep efficiency (min)	82 (78, 95)	94 (92, 97)	.046*	.44
Sleep latency (min)	44 (20, 46)	15 (13, 23)	.026*	.48
Wake after sleep onset (min)	96 (32, 129)	29 (19, 41)	.024*	.49
Activity index	60 (38, 68)	39 (36, 49)	.079	.39
# Contiguous wake epochs	15 (14, 29)	11 (7, 14)	.009**	.55
Mean wake episode (min)	6 (4, 11)	5 (4, 6)	.287	.24
Longest wake episode (min)	39 (21, 48)	18, (15, 29)	.031*	.47
# Contiguous sleep epochs	14 (13, 28)	11 (6, 13)	.009**	.55
Mean sleep episode (min)	29 (17, 50)	57 (39, 108)	.038*	.46
Longest sleep episode (min)	125 (80, 191)	178 (127, 268)	.144	.33

\*significant at  $p < .05$  \*\*significant at  $p < .01$

Table 5 compares 14 day averages of each sleep diary parameter for three age groups. One way ANOVA's were conducted on each normally distributed parameter, with mean and SD reported. Kruskal Wallis tests were conducted on parameters with non-normal distributions, with median and 25<sup>th</sup>, 75<sup>th</sup> percentiles reported. Most interesting are the sleep diary parameters that did not show significant differences that typically should resolve with age (e.g., sleep latency, not sleeping in own bed, awakening through the night). As expected, Group 3 (12-17 years) had less average hours in bed at night, and Group 1 (3-6 years) had more naps. Group 1 and Group 2 (7-11 years) had more nights that they moved; surprisingly, no significant group difference occurred between them ( $\alpha$  at .017). Group 2 and Group 3 had more nights that typical routine did not occur. A follow up independent *t*-test identified Group 2 as having significantly more nights with an atypical bedtime routine ( $p = .009$ ) compared to Group 1.

**Table 5 Comparison of Sleep Diary Parameters across Age Groups (N = 95)**

<b><u>Sleep Parameter</u></b>	<b><u>Ages 3-6 (n = 41)</u></b>	<b><u>Ages 7-11 (n = 39)</u></b>	<b><u>Ages 12-17 (n = 15)</u></b>	<b>Sig. Difference (<math>p &lt; .05</math>)</b>
Average bedtime (PM) <sup>a</sup>	8.40 (0.6)	8.60 (0.6)	9.15 (0.7)	.001
Average awake time (AM) <sup>a</sup>	6.77 (0.7)	6.72 (0.6)	6.88 (0.5)	
Average hours in bed <sup>a</sup>	10.4 (0.8)	10.2 (0.4)	9.7 (0.6)	.011
# Irregular bedtimes	5 (3,7)	6 (4,7)	5 (2,7)	
# Nights latency occurred	4 (0,7)	2 (1,5)	2 (0,10)	
# Nights not in own bed	0 (0,1)	0 (0,5)	0 (0,2)	
Total # of awakenings	4 (2, 8)	3 (0,14)	0 (0,7)	
# Nights awakenings occurred	4 (2, 7)	2 (0,8)	0 (0,7)	
# Nights moved	1(0, 2)	0 (0,3)	0 (0,0)	.033
# Irregular awake times	5 (3, 8)	6 (4,8)	4(3,7)	
# of difficult awakenings	1 (0, 2)	0 (0,1)	0 (0,1)	
# of days naps taken	1 (0, 6)	0 (0,1)	0 (0,0)	.005
# of naps	1 (0, 5)	0 (0,0)	0 (0,0)	.003
# nights not typical routine	2 (0, 3)	3 (2,5)	2 (1,5)	.047

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<sup>a</sup> First three parameters are normal distributions with mean (SD) per age group.

Last, descriptive information regarding medication usage collected from the sleep diaries identified 3 participants (7%) of age Group 1, 13 participants (33%) of age Group 2, and 3 participants (20%) of age Group 3 as taking medication daily for sleep. Of these 19 children, 16 (84%) had a full mutation, 16 (84%) were males, and 10 (53%) had *CSHQ* scores ( $\geq 41$ )

indicating significant sleep problems despite taking daily medications to assist with sleep. Medications included melatonin (8), clonidine (3), risperdol (1), seroquel (1), abilify (1), remeron (1), buspirone (1), and a combination of these medications (3).

To test Hypotheses 2, that problematic sleep patterns are positively associated with caregiver's negative mood, a one-tailed Spearman correlation coefficient was computed between *CHSQ* scores and mood ratings. In addition, Generalized Estimating Equation (GEE) was conducted on the repeated data collected via the two-week sleep diary. The Generalized Estimating Equations "produce more efficient and unbiased regression estimates" when analyzing longitudinal or repeated measures data on non-normal distributions. GEEs account for within-subject correlation of responses and can test main and interaction effects of categorical or continuous independent variables (Ballinger, 2004). The model determined within subject correlation and main effects of each mood rating (sad/happy, angry/pleasant, and overwhelmed/relaxed) and overall average mood of caregiver with each of the following 10 sleep categories entered separately as dependent variables: typical bedtime, sleep latency, own bed, awakenings, moved, amount of sleep, typical awake time, difficulty awakening, medication, and whether typical bedtime routine occurred. All probability distributions were binomial except amount of sleep which was normally distributed. Exchangeable was chosen as the working correlation matrix structure for two reasons. First, no previous research exists on which to base the structure and literature does not provide much insight on how to choose a good working correlation. Secondly, exchangeable is preferred for cross sectional design and assumes that the within subject correlations are constant over time. It also controls for multiple responses within a subject by assuming a common correlation between any two responses.

To review, each caregiver present at bedtime indicated how s/he felt prior to their child's bedtime on a 10-point range contrasting three sets of emotions (sad/happy, angry/pleasant, and overwhelmed/relaxed). Higher scores indicated a more positive mood. To maintain independent sampling, one caregiver report belonging to a sibling pair was randomly excluded from the analysis. Table 6 provides average and minimum scores for each mood range for Caregiver 1 (79) and Caregiver 2 (50) per age group. The maximum possible score of 10 was reported by all caregivers and all moods.

**Table 6 Mean (Minimum Score<sup>a</sup>) of Caregiver Mood per Age Group**

	<b>Ages 3-6</b>	<b>Ages 7-11</b>	<b>Ages 12-17</b>
<b>Caregiver 1</b>	<b><u>n = 34</u></b>	<b><u>n = 33</u></b>	<b><u>n = 12</u></b>
Sad/Happy	8.3 (5.7)	8.5 (5.8)	8.2 (6.8)
Angry/Pleasant	8.1 (2.2)	8.3 (5.2)	8 (6.6)
Overwhelm/Relax	7.8 (2.1)	7.9 (4.5)	7.9 (4.6)
Overall mood	8 (4.5)	8.2 (5.7)	8.2 (6.3)
 <b>Caregiver 2</b>	 <b><u>n = 26</u></b>	 <b><u>n = 17</u></b>	 <b><u>n = 7</u></b>
Sad/Happy	8.1 (5.7)	8.5 (7)	8.5 (6.6)
Angry/Pleasant	7.8 (2.4)	8.3 (4.6)	8.5 (6.2)
Overwhelm/Relax	7.6 (2)	8.2 (4.6)	8.1 (5.4)
Overall mood	7.9 (4.5)	8.3 (5.7)	8.3 (6.1)

<sup>a</sup> all maximum scores were equal to 10

Hypothesis 2 predicts an inverse relation between problematic sleep patterns and caregiver mood. A one-tailed Spearman correlation coefficient ( $n = 79$ ,  $\alpha$  at .05) identified significant negative correlations between total *CHSQ* scores (higher scores indicating more problematic sleep patterns) and average overall mood of Caregiver 1 ( $r = -0.20$ ,  $p = .04$ ); and

*CSHQ* score and average overwhelmed vs. relaxed mood of Caregiver 1 ( $r = -0.25$ ,  $p = .01$ ). Sad/Happy mood ( $p = .08$ ) and Angry/Pleasant mood ( $p = .07$ ) were not reliably associated with *CSHQ* total score. No significant correlations occurred for Caregiver 2 mood and total score of *CSHQ* ( $n = 50$ , *ns*).

A GEE regression analysis computed for each mood rating of Caregiver 1, over 13 days, as the predictor variable for 10 sleep diary parameters identified lower overall mood as a significant predictor of longer sleep latency ( $p = .02$ ) and overwhelmed mood as a significant predictor of both longer sleep latency ( $p = .005$ ) and more time in bed ( $p = .02$ ).

Covariates of child age and gender, family income, educational level of caregiver, and number in household were entered into the significant equations. Overall lower average mood ( $p = .05$ ) and overwhelmed mood ( $p = .007$ ) continued to be significant predictors for longer sleep latency. Younger age ( $p = .045$ ) was a significant predictor of more time in bed. Overwhelmed mood became less significant ( $p = .10$ ) for amount of time in bed.

No significant prediction was found using Caregiver 2 mood.

To test Hypothesis 3, that regular bedtime routine will be positively associated with lower levels of problematic sleep patterns, a one-tailed Spearman correlation coefficient was computed between total *CHSQ* score and total number of irregular bedtimes recorded in diary. GEE was conducted by entering typical bedtime routine as the binary predictor variable with nine of the sleep diary parameters each entered as a dependent variable. Exchangeable continued as the correlation matrix structure.

A one-tailed Spearman correlation coefficient ( $N = 95$ ;  $\alpha$  at .05) identified a significant positive correlation between the total *CHSQ* score and number of irregular bedtimes ( $p = .017$ ). GEE analysis ( $n = 81$ ), with typical bedtime routine as the predictor of 9 sleep diary parameters,

revealed that an inconsistent bedtime routine significantly predicted: an irregular bedtime ( $p = .000$ ); the child not going to sleep in own bed ( $p = .04$ ); a greater amount of time in bed ( $p = .009$ ); an atypical awake time ( $p = .001$ ); and, unexpectedly, the child not having difficulty waking in the morning ( $p = .007$ ). These results remained unchanged when family income and caregiver education were entered as covariates.

To test Hypothesis 4, that children with FXS who have a greater number of CGG repeats will have more sleep problems and a closer association between sleep problems and parent negative mood and changes in bedtime routine, a Pearson's chi-square test statistic was conducted between *CSHQ* and mutation status both as a binary variables; also a Mann-Whitney test was conducted comparing between-group means of total *CSHQ* score and mutation status. A GEE was conducted with mutation status as the predictor variable on the ten sleep diary parameters.

Neither the Mann-Whitney test conducted on the *CHSQ* total scores nor the Pearson Chi-square statistic conducted on *CSHQ* as a binary variable, revealed significant findings with mutation status. The GEE multivariate analysis identified mutation status ( $p = .007$ ) as a significant predictor of amount of time in bed. An additional GEE analysis was conducted with mutation status as the predictor variable on 10 diary sleep parameters. Full mutation status predicted more time in bed (.002) and less difficulty waking in the morning (.027).

## **5.0 DISCUSSION**

The aim of this study was to explore patterns of sleep for children with FXS in relation to parent mood. This is the first study to describe sleep in a relatively large sample of children (N = 95) with FXS within the home environment using both subjective and objective methods of data collection. The information gained from this research study adds compelling evidence and knowledge to the existing, but scant, body of literature on sleep characteristics of children with FXS.

### **5.1 SUMMARY OF RESULTS**

Hypothesis 1- Caregivers (48%) reported that their children with FXS had prevalent sleep problems at a level worthy of a referral to a sleep clinic. Few children (20%) were given medication to ameliorate sleep problems, 53% of those children receiving medication continued to score in the clinical range of sleep problems on the *CSHQ* measure. Pilot actigraph findings revealed significant differences in sleep parameters for children with FXS compared to a normal control group. Finally, the majority of sleep parameters measured in the diary and on the *CSHQ* did not show age group or family characteristic differences. This may be due to homogeneity or size of sample; the non-significant association of these child or family demographic variables will need to be investigated further.



Hypothesis 2 – Lower overall mood and overwhelmed mood reported by Caregiver 1 were significantly correlated with his or her report of higher *CSHQ* scores. Caregiver 1's lower overall mood covaried with sleep latency in the child and overwhelmed mood of Caregiver 1 covaried with both sleep latency and more time in bed for the child. In multivariate analysis with statistical control of demographic variables, overwhelmed mood became less significant and younger age became a stronger predictor of more time in bed.

Hypothesis 3 - A significant correlation emerged between total *CSHQ* score and number of irregular bedtimes reported by caregiver. An inconsistent bedtime routine predicted an irregular bedtime, that child did not go to sleep in own bed, a greater amount of time in bed, an atypical awake time, and that child did not have difficulty waking for the day.

Hypothesis 4 – Full mutation status predicted more time in bed and less difficulty waking in the morning.

### **5.1.1 Descriptive Data on Sleep Problems**

Based on information from the *CSHQ*, parents reported nearly half (48%) of their children with FXS had sleep problems of a magnitude sufficient to suggest the need for a referral to a sleep center; another 28% of the parents reported problems were significant but less extreme. Owens and colleagues (2000) noted that each subscale (e.g., bedtime resistance, sleep anxiety) on the *CSHQ* should be examined even for a child who has a low total score to ascertain whether that child has sleep disturbances that may warrant additional care. Using the total score and examining individual items that were considered prevalent within subscales, this study demonstrates that parents of children with FXS report many sleep-related problems on the *CSHQ*.

The literature on sleep patterns for children within the general population, compared to findings from this study, illustrate where children with FXS fall on the continuum of sleep in the general pediatric population. Liu, Liu, Owens, and Kaplan (2005) utilized the *CSHQ* to compare sleep patterns in school-age children (grades 1 to 4) in China (n = 292) and the United States (n = 415). As in the current study, the authors defined prevalent sleep problems as occurring “sometimes” or “usually” in at least 20% of the sample. Thirteen items were thus classified as prevalent among the US children as compared to 21 items in this study of children with FXS; 12 prevalent items were similar in both studies. Comparing US children to those with FXS in the same age category (7-11 years) several salient item differences occur (US vs. FXS): “alarmed by scary dream,” 1% vs. 23% (23 fold difference); “awakens more than once,” 2.5% vs. 31% (12 fold difference); “sleep latency,” 21% vs. 33%; “awakens once during night,” 25% vs. 51%; “restless and moves a lot,” 35% vs. 59%; “grinds teeth,” 21% vs. 36%; and “seems tired during day,” 24% vs. 39%. The US children scored notably higher than children with FXS on several items about morning waking: “others wake child,” 68% vs. 36%; “hard time getting out of bed,” 39% vs. 19%; and “awakens in negative mood,” 34% vs. 18%. Although children with FXS appear to have less difficulty at morning waking, it may be a precipitating factor that leads to the prevalent items reported in the subcategory of daytime sleepiness on the *CSHQ*. Children with FXS in the current study clearly demonstrated higher levels of sleep disturbing behaviors compared to their peers in the typical population.

The present study also included comparing all 21 prevalent items on the *CSHQ* across the three age groups and showed that sleep issues in children with FXS are present at an early age but may not resolve over time or with age (e.g., night awakenings, trouble sleeping away from home, talking during sleep, sleep latency). Only in the oldest age group (12-17 years) did several

items significantly diminish (e.g., bedwetting, grinding teeth, sleepy while riding in the car).

These data suggest that sleep problems should be addressed early among children with FXS, and not dismissed as a consequence of the syndrome. The implementation of a systematic clinical interview targeted at sleep behaviors in this population would enhance research and clinical care and comply with recommendations of the National Commission on Sleep Disorders Research.

Based on pivotal findings from a 1992 sleep study performed in the United States entitled **Wake up America: A National Sleep Alert**, the commission found no population subgroup sufficiently aware of the consequences of sleep deprivation. Just as importantly, the commission uncovered serious gaps in sleep research. Primary care providers, as well as the general public, needed information to understand and treat sleep problems. At the strong recommendation of the commission, the National Sleep Foundation was established to promote education and research to expand public awareness. It is vital that clinicians are prepared to diagnose and treat sleep problems in all children but especially those with developmental disabilities who demonstrate higher levels of sleep disturbance (Johnson, 1996; Quine, 2001; Richdale 2003; Schreck & Mulick 2000).

Both typically and atypically developing children are able to establish good sleep habits when structure and routine are established at bedtime (Durand, 1998; Stores & Wiggs, 2001). Children with FXS appear no different in this respect as an inconsistent bedtime routine was a significant correlate of several variables (i.e., child not going to sleep in own bed, atypical awake time, less difficulty waking in morning). Children with FXS are very sensitive to environmental stimuli. Therefore, a change in routine possibly triggers irregularities in behavior and arousal. Events in the evening that many of us accept as typical occurrences (e.g., guests over for dinner, a movie, or even a parental argument) may trigger bedtime resistance, anxiety, or night

awakenings. One intervention study involving children with FXS saw reduction of sleep problems after implementing a parent training program that assisted families in implementing an effective bedtime routine, included elements of applied behavior analysis, and introduced standard extinction techniques to resolve sleep disrupted behaviors (Weiskop, Richdale, & Matthews, 2005). Additional intervention studies are warranted in this area.

### **5.1.2 Use of Sleep Medication**

The present study gathered descriptive information on current medication use to ameliorate sleep problems. Only 19 of the 95 (20%) children took medications to induce sleep. Of note, 11 of the 19 (58%) children receiving sleep medication scored in the clinical range on the *CSHQ*, suggesting continued problems. Several questions arise from these findings: Are those medications being prescribed not helpful or not monitored sufficiently to be effective?

In addition, most children with FXS in this study were not prescribed medications, but were having significant sleep problems. Is pharmacotherapy an underexplored option in the treatment of sleep problems among children with FXS? What individual or family characteristics enhance or reduce the use or effectiveness of medication for sleep? There are few investigations of pharmacotherapy in treating sleep disturbances of children in general and fewer involving children with developmental disabilities. Melatonin appears to be the most widely investigated medication in children with intellectual disabilities to enhance sleep (Giannotti, Cortesi, Cerquiglini, & Bernabei, 2006; Jan, 2000; Pillar, Sharar, Peled, et al., 2000; Sajith & Clarke, 2007; Turk, 2003; Wirojatanan, Jaquemont, Goodlin-Jones, Dioux, Anders, & Hagerman,

2007). To further investigate the efficacy of sleep medications, there is a need for double blind, cross-over design studies that enroll significant numbers of children so that families and clinicians have scientific data on which to make informed treatment decisions. Similar arguments are relevant for studying behavioral strategies to improve sleep.

### **5.1.3 Actigraphy**

The pilot actigraphy data from this study demonstrated that children with FXS have significantly different and more disturbed sleep patterns than a normal comparison group matched on age. Although the actigraph provides objective and scientifically sound measurements of sleep, both compliance from and tolerance of the device by children with FXS were a challenge. The compliance rate in this study was only 45%. Another recent study involving children with autism and FXS measured the effects of melatonin using actigraphy. Only 12 of 18 participants (66%) used the device (Wirojatanan et al., 2007). Ways to improve participation and compliance need to be explored further. One option is to implement a behavior modification session with the child simulating what is expected and providing positive reinforcement for cooperation. Another option is to devise creative ways of attaching the actigraph to pajamas rather than the wrist to increase cooperation. Obtaining more objective and representative data will go a long way toward establishing a body of knowledge on sleep patterns in children with FXS on which to base future intervention studies.

#### 5.1.4 Caregiver Mood

By examining sleep in relation to caregiver mood, the relationship between a child's sleep and family functioning begins to unfold. A reported feeling of being overwhelmed on the part of the primary caregiver of the child with FXS significantly covaried with longer sleep latency and amount of time in bed for the child with FXS. Higher *CSHQ* scores were significantly correlated with overall poorer mood of the primary caregiver, as well as feeling overwhelmed. Although the hypothesis posited a direct association, in reality sleep and family functioning probably have a complex bi-directional interaction. A few recent studies, using various samples of children, also identified child sleep disruptions and/or maternal quality of sleep as significant correlates of mothers feeling overloaded and burned out (Meltzer & Mindell, 2007), of marital conflict (El-Sheikh, Buckhalt, Mize, & Acebo, 2006), and of negative parent mood, parenting hassles, and disruptions in bedtime routines (Fiese, Winter, Sliwinski, & Anbar, 2007). Continued investigation using a broad range of subjective and objective measures of sleep patterns and family functioning will be required "for advancing our understanding of sleep and health within a family context" (Dahl & El-Sheikh, 2007, p. 2) and to lay the foundation for establishing effective interventions to reduce effects of sleep problems. Intensive qualitative investigation may be needed to clarify causal processes that may work bi-directionally between family stressors and child sleep disruptions.

### 5.1.5 Limitations

There are some methodological limitations to this study. First, the design of this project was cross-sectional. A longitudinal, repeated measures design would permit a more complex and accurate presentation of the associations among variables.

Second, data collection included both subjective and objective measures. Although this can strengthen a study design there are several cautions warranted. In the first place, subjective and objective measures capture different aspects of a phenomenon, and can have limited interface. Overgeneralizing from results of either kind of measure can misrepresent the full nature of the phenomenon. On the other hand, direct comparison of conflicting results may obfuscate relatively straightforward—but competing—causal processes at work. Finally, caregiver reports reflect caregiver needs, concerns, and biases as much as the objective phenomenon they are designed to assess. Respondents may have habituated to the 14 day diary therefore using the sleep diary for several intermittent collections rather than 14 continuous days may eliminate both responder habituation to the measure and confounds to the cross sectional time frame (e.g., disruptions related to daylight savings time, illness).

Third, recruitment was not random therefore the sample may have been artificially homogeneous and non-representative of the FXS population. All but one respondent were female; most caregivers were of higher SES and education level, and were married. Patterns relating to caregiver moodiness and bedtime routine disruptions may be more pronounced in a population typically having a more consistent day-to-day schedule and a less chaotic homelife.

Fourth, several child-related variables were not considered in the study's design, including use of medication for daytime behaviors, co-morbid medical or psychological conditions, and child's cognitive level.

Fifth, the study lacked a comparison group. Although the literature was able to provide some comparison points to sleep in children with other disabilities and the general population, this study would have furnished more definitive results if a demographically matched comparison group had been included. Even actigraphy results may be misleading, since the comparison group was matched only on child age.

Sixth, actigraphy was piloted on a very small, presumably unrepresentative subsample of children with FXS. Compliance and tolerance of the actigraph was limited.

Seventh, although sample size ( $N = 95$ ) was sufficient to detect a medium effect, power for GEE multivariate analyses was minimally sufficient based on at least 10 subjects per each variable entered. The degree to which conclusions can apply to the entire FXS population is severely limited.

#### **5.1.6 Future Investigations**

Future studies should involve greater use of actigraphy to expand on the pilot information gained here. Polysomnography is an additional bio-physical measurement to employ in future investigations to obtain information on stages of sleep and underlying neurophysiologic mechanisms. Subjective questionnaires should continue; they provide an opportunity for families to identify sleep habits viewed as a detriment to family functioning. Future studies should explore interventions that increase positive emotions, but not emotional arousal, in the family at bedtime, and assist in the establishment and maintenance of successful bedtime routines. Given the indirect evidence uncovered here that sleep medications lack efficacy in this population, behavioral interventions may be the best first course of action, both in research and in practice. These should be based on goals established by the family around their identification of problem



areas. Pharmaceutical interventions must be based on empirical research and evidenced based practice guidelines that have yet to be developed. Effectiveness of sleep medications must be closely monitored using reliable objective measures. There may be a real danger of inappropriately medicating sleep problems in this and other special needs populations.

### **5.1.7 Conclusions**

In summary, the current findings suggest that many parents of children with FXS report problematic sleep patterns that are associated with parent reported mood and bedtime routines. Many prevalent sleep problems identified in this study did not follow a typical developmental pattern; the cross sectional data suggest these problems are not resolving with age, potentially acting as a chronic stress in the home environment for years. All families of sleep disrupted children are at some risk for subsequent physical and emotional distress; however, families of children with FXS may be at even higher risk due to the challenges this syndrome already places on families.

In this study, sleep issues emerged regardless of income, educational level, household size, or even sleep medication. Therefore, every family with a child having FXS may experience the effects of sleep deprivation. These data are concordant with other studies on children with neurodevelopmental disabilities (Quine, 2001; Richdale et.al, 2000; Schreck & Muleck, 2000). Results indicate that routine clinical care of children with FXS should include careful screening of sleep, but that medication should not automatically be prescribed as a solution. Additional research is needed to identify specific problems with sleep in order to initiate clinical trials focusing on behavioral, as well as pharmaceutical, interventions aimed at key sleep parameters.

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