The trajectories of sleep disturbances in Rett syndrome

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SUMMARY

Rett syndrome is a rare neurodevelopmental disorder usually affecting females, and is associated with a mutation in the *MECP2* gene. Sleep problems occur commonly and we investigated the trajectories and influences of age, mutation and treatments. Data were collected at six time points over 12 years from 320 families registered with the Australian Rett Syndrome Database. Regression analysis was used to investigate relationships between sleep disturbances, age, mutation type and use of treatment, and latent class growth analysis was performed to identify sleep problem phenotypes and model the effect of mutation type. The age range of subjects was 2.0–35.8 years. The study showed that sleep problems occurred in more than 80% of individuals and the prevalence decreased with age. Night laughing and night screaming occurred in 77 and 49%, respectively, when younger. Those with a large deletion had a higher prevalence of night laughing, which often occurred frequently. Treatment was associated with a 1.7% reduction in risk of further sleep problems. High and low baseline prevalence groups were identified. Approximately three-quarters of girls and women with sleep disturbances were in the high baseline group and problems persisted into adulthood. Conversely, 57% with night laughing and 42% with night screaming in the high baseline group exhibited mild improvement over time. Mutation type was not found to be a significant predictor of group membership. In conclusion, the evolution of sleep problems differed between subgroups of girls and women with Rett syndrome, in part explained by age and genotype. Treatment was not associated with improvement in sleep problems.

INTRODUCTION

Rett syndrome is a neurodevelopmental disorder usually associated with a mutation on the methyl CpG binding protein 2 (*MECP2*) gene (Amir *et al.*, 1999), characterized initially by loss of communication and hand function skills and the development of hand stereotypies and impaired gait (Neul *et al.*, 2010). The severity of symptoms and comorbidities, for example in relation to hand function, mobility, scoliosis and epilepsy, varies across individuals, and certain mutations (p.R133C, p.R294X and p.R306C) are associated with milder phenotype while others (p.T158M, p.R168X, p.R255X, p.R270X and large deletion) are linked to more severe clinical presentation (Bebbington *et al.*, 2008; Cuddapah *et al.*, 2014). Early literature on Rett syndrome described the occurrence of sleep dysfunction manifesting initially as screaming or night laughing in the young child (Hagberg, 1995, 2002, 2005; Naidu *et al.*, 1986), and was believed to be associated with immature sleep patterns (Nomura, 2005). As a consequence, impaired sleep was originally included (Hagberg *et al.*, 2002) and has been retained as a supportive criterion in the current diagnostic criteria (Neul *et al.*, 2010).

Sleep dysfunction in Rett syndrome was described in an early US clinic-based sample (n = 20) published in 1990. Total sleep duration was longer than in age-matched typically developing peers (Piazza *et al.*, 1990). Delayed sleep onset, shorter night sleep with night-waking and persisting daytime sleeps were also reported, and sleep patterns appeared to worsen with age. Using a subset of the Australian population-based data, persistence of daytime napping with increasing

Table 1 Frequency and prevalence of sleep problems by age group and year of questionnaire*

	Year of questionnaire [n (%)]					
Age group (years)	*2000 (n = 159)*	*2002 (n = 189)*	*2004 (n = 203)*	*2006 (n = 208)*	*2009 (n = 221)*	*2011 (n = 220)*
Any sleep problem						
0–7	33 (94.3)	29 (85.3)	34 (94.4)	31 (93.9)	22 (91.7)	31 (93.9)
8–12	40 (93.0)	43 (81.1)	40 (87.0)	36 (81.8)	39 (92.9)	30 (79.0)
13–17	42 (97.7)	46 (95.8)	37 (78.7)	40 (87.0)	36 (83.7)	32 (84.2)
18+	32 (88.9)	48 (90.6)	61 (88.4)	71 (88.8)	91 (85.5)	79 (73.2)
Night laughing						
0–7	21 (60.0)	27 (79.4)	28 (77.8)	29 (87.9)	20 (87.0)	24 (75.0)
8–12	30 (69.8)	33 (63.5)	35 (76.1)	26 (63.4)	27 (67.5)	23 (62.2)
13–17	33 (78.6)	42 (87.5)	34 (73.9)	32 (72.7)	30 (69.8)	22 (57.9)
18+	23 (63.9)	39 (72.2)	44 (62.9)	53 (66.3)	61 (59.8)	50 (49.0)
Night screaming						
0–7	8 (22.9)	18 (52.9)	23 (63.9)	20 (60.6)	10 (43.5)	17 (53.1)
8–12	14 (32.6)	25 (47.2)	23 (50.0)	16 (37.2)	18 (46.2)	15 (40.5)
13–17	19 (46.3)	23 (47.9)	20 (44.4)	17 (37.8)	12 (27.9)	10 (27.0)
18+	9 (26.5)	28 (53.9)	28 (39.4)	32 (40.5)	44 (42.7)	39 (37.1)
Night waking						
0–7	–	–	–	28 (93.3)	20 (87.0)	25 (89.3)
8–12	–	–	–	30 (79.0)	33 (91.7)	21 (72.4)
13–17	–	–	–	34 (85.0)	29 (78.4)	20 (71.4)
18+ y	–	–	–	57 (85.1)	76 (78.4)	55 (64.0)

*Prevalence was calculated based on sample size that excluded missing data.

Table 2 Frequency and prevalence of specific sleep problems by occurrence frequency and year of questionnaire*

	Year of questionnaire [n (%)]					
Frequency scale	*2000 (n = 159)*	*2002 (n = 189)*	*2004 (n = 203)*	*2006 (n = 208)*	*2009 (n = 221)*	*2011 (n = 220)*
Night laughing						
Did not occur	49 (31.4)	47 (25.0)	57 (28.8)	58 (29.3)	70 (33.7)	90 (43.1)
Sometimes	61 (39.1)	66 (35.1)	72 (36.4)	78 (39.4)	83 (39.9)	69 (33.0)
Often	46 (29.5)	75 (39.9)	69 (34.9)	62 (31.3)	55 (26.4)	50 (23.9)
Night screaming						
Did not occur	103 (67.3)	93 (49.7)	104 (52.5)	115 (57.5)	124 (59.6)	130 (61.6)
Sometimes	31 (20.3)	49 (26.2)	50 (25.3)	51 (25.5)	45 (21.6)	43 (20.4)
Often	19 (12.4)	45 (24.1)	44 (22.2)	34 (17.0)	39 (18.8)	38 (18.0)
Night waking						
Did not occur	–	–	–	26 (14.9)	35 (18.1)	50 (29.2)
Sometimes	–	–	–	27 (15.4)	24 (12.4)	26 (15.2)
Often	–	–	–	122 (69.7)	134 (69.4)	95 (55.6)

*Prevalence was calculated based on sample size that excluded missing data.

age was also confirmed as were delayed sleep onset and night waking, but the proportion of total sleep at night did not decrease with age (Ellaway *et al.*, 2001). In a more recent total Australian population-based study, sleep dysfunction was noted in approximately 80% of girls and women under 30 years of age, and specific symptoms such as night laughing and night screaming were reported to occur in approximately 60 and 35% respectively (Young *et al.*, 2007). In the same study we also found that the prevalence of night laughter decreased with age and sleep problems were more likely in those with certain genotypes such as large deletion, p.R294X or p.R306C mutation. There is a need for further longitudinal analyses to better understand the natural history of sleep dysfunction in Rett syndrome.

Management of sleep disturbance in children and adults with developmental disorders includes behavioural and pharmacological strategies, but the evidence base in Rett syndrome is limited. One single case design study ($n = 3$) tested behavioural strategies during short inpatient hospital stays, and improvements in regularity of sleep pattern were achieved (Piazza *et al.*, 1991). Shorter time to sleep onset has been observed with 5-hydroxytryptophan, a metabolic intermediate in the synthesis of serotonin and melatonin, in five of seven cases when used over approximately

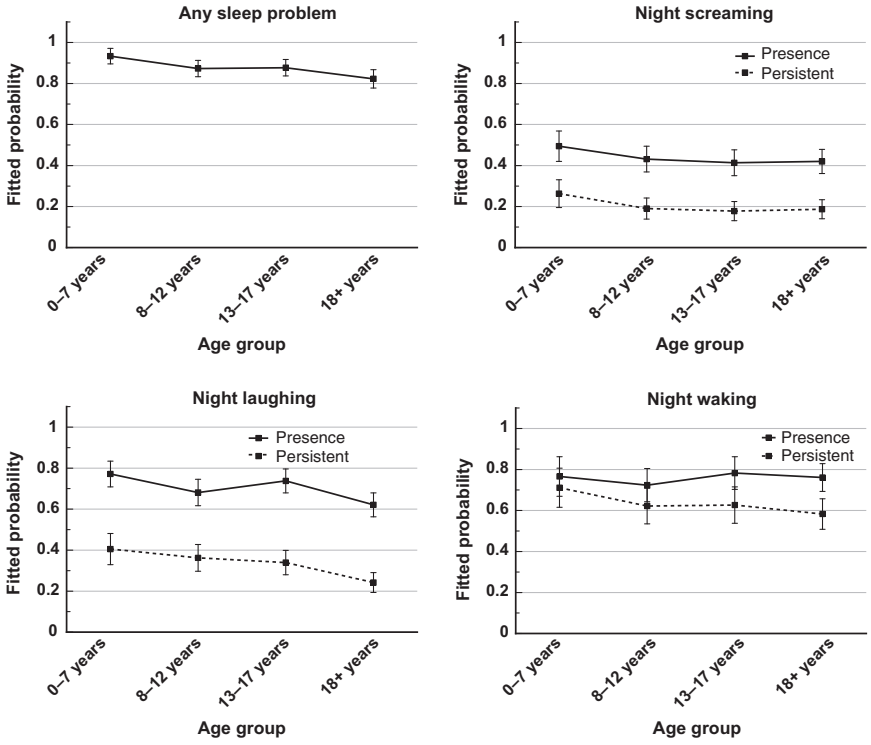

Figure 1. Fitted probabilities of any sleep problem, night laughing, night screaming and night waking, by age group. Night waking: analysis based on three time points (2006, 2009 and 2011) as compared to six time points for any and specific sleep problems.

Table 3 Frequency and prevalence of mutation type by questionnaire year*

	Year of questionnaire [n *(%)]*					
Mutation type	*2000* (n = *159)*	*2002* (n = *189)*	*2004* (n = *203)*	*2006* (n = *208)*	*2009* (n = *221)*	*2011* (n = *220)*
No mutation	33 (21.9)	44 (24.3)	41 (21.0)	43 (21.5)	39 (18.6)	36 (17.5)
C-terminal	12 (8.0)	12 (6.6)	15 (7.7)	17 (8.5)	20 (9.5)	18 (8.7)
Early truncating	7 (4.6)	10 (5.5)	8 (4.1)	7 (3.5)	10 (4.8)	10 (4.9)
Large deletion	5 (3.3)	8 (4.4)	10 (5.1)	11 (5.5)	12 (5.7)	12 (5.8)
p.R106W	3 (2.0)	2 (1.1)	4 (2.1)	7 (3.5)	7 (3.3)	9 (4.4)
p.R133C	8 (5.3)	10 (5.5)	11 (5.6)	11 (5.5)	18 (8.6)	18 (8.7)
p.R168X	15 (9.9)	16 (8.8)	19 (9.7)	15 (7.5)	14 (6.7)	17 (8.3)
p.R255X	8 (5.3)	8 (4.4)	11 (5.6)	11 (5.5)	15 (7.1)	12 (5.8)
p.R270X	12 (8.0)	14 (7.7)	14 (7.2)	13 (6.5)	15 (7.1)	14 (6.8)
p.R294X	10 (6.6)	12 (6.6)	15 (7.7)	15 (7.5)	15 (7.1)	13 (6.3)
p.R306C	7 (4.6)	9 (5.0)	10 (5.1)	11 (5.5)	9 (4.3)	10 (4.9)
p.T158M	14 (9.3)	16 (8.8)	16 (8.2)	17 (8.5)	18 (8.6)	20 (9.7)
Other	17 (11.3)	20 (11.1)	21 (10.8)	22 (11.0)	18 (8.6)	17 (8.3)

*Prevalence was calculated based on sample size that excluded missing data.

18 months (Nomura *et al*., 1985). In a randomized cross-over trial of melatonin (n = 9) time to sleep onset decreased, but there was no change in the frequency of night waking (Mcarthur and Budden, 1998). Disrupted sleep is likely to have a large burden on the health and wellbeing of both the child and family affected by Rett syndrome (Mcdougall *et al*., 2005), yet our insight into how to manage sleep dysfunction is remarkably limited.

Using longitudinal data contained in the Australian Rett Syndrome Database, we determined the prevalence of sleep problems in Rett syndrome and investigated determinants of the trajectories of sleep problems in Rett syndrome, including age, *MECP2* mutation and use of treatment.

METHODS

Study population and data ascertainment

Established in 1993, the Australian Rett Syndrome Database is a longitudinal and population-based registry of confirmed cases with Rett syndrome born since 1976 (Downs *et al*., 2008). Follow-up questionnaires were distributed to parents/

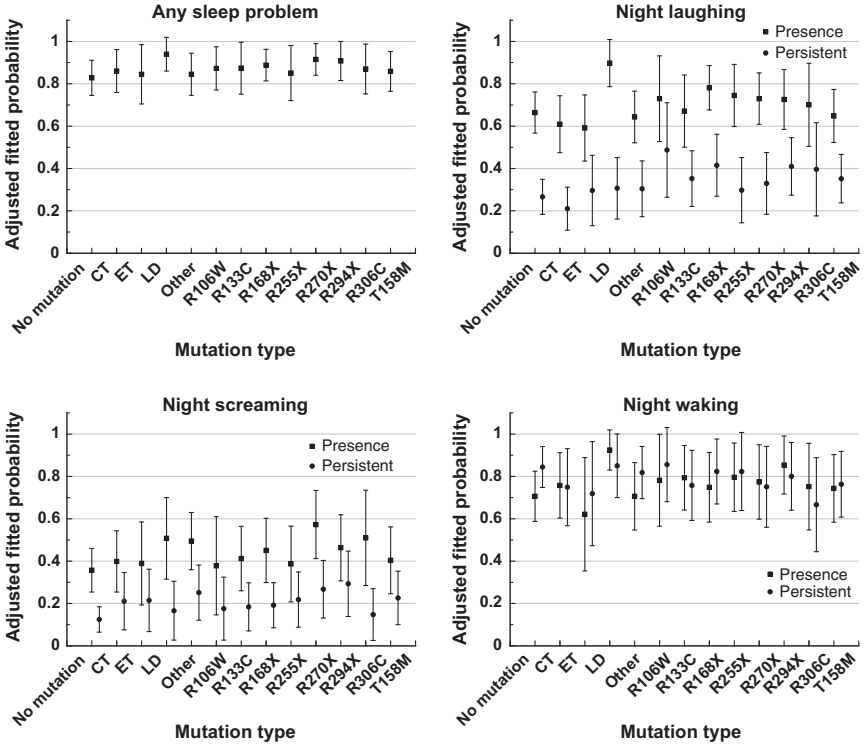

Figure 2. Aged adjusted fitted probabilities of any sleep problem, night laughing, night screaming and night waking, by mutation type. Night waking: analysis based on three time points (2006, 2009 and 2011) as compared to six time points for any and specific sleep problems. CT, C-terminal deletions; ET, Early truncating; LD, Large deletion.

carers in 2000, 2002, 2004, 2006, 2009 and 2011 (Leonard *et al*., 2010). Females who were clinically (Neul *et al*., 2010) or genetically confirmed and whose parents/carer had completed at least one of the follow-up questionnaires were eligible for the study. Data were available from 320 cases.

Ethical approval of this study was obtained from the Human Research Ethics Committee of Princess Margaret Hospital for Children, Western Australia (1909/EP).

Sleep-related variables

Parents or carers were asked at each time point if their daughter had had any sleep problems since the last questionnaire. Data were available from 2000 on the presence and frequency of any sleep problems, night laughing and night screaming, and from 2006 for night waking. For each aspect of sleep, the frequency was described as 'did not occur', 'sometimes' (recorded as 'less than once a month', 'monthly' or 'twice a month') or 'often' (recorded as 'weekly or more' or 'nightly). The data were supplemented where necessary with two items from the Rett Syndrome Behaviour Questionnaire (Mount *et al*., 2002): 'spells of laughter for no apparent reason during the night' (night laughing) and 'spells of screaming for no apparent reason during the night' (night screaming). For analyses, two binary variables were generated: 'presence of sleep problem' by combining the levels 'sometimes' and often' and compared with 'did not occur'; and 'persistent sleep problem' using the level 'often' and compared with the combined levels 'did not occur' and 'sometimes'. Any and specific sleep problems were considered unresolved if the problem, as represented by the variables 'presence of sleep problem' and 'persistent sleep problem', continued to the next time point. Conversely, if no sleep problems were reported at the next time point, the conditions were considered resolved.

Respondents were also asked about the ongoing treatment (s) used for the individual's sleep problems at each time point. The treatments were grouped into five categories: (i) sleep medications: melatonin, nitrazepam, temazepam, oxazepam, clonidine, chloral hydrate and hypnotics; (ii) non-specific sleep medications: anti-epileptic drugs, risperidone, haloperidol, olanzapine, promethazine, trimeprazine, amitriptyline, fluoxetine, mirtazapine and medications that alleviated symptoms affecting sleep; (iii) non-pharmaceutical treatments; (iv) more than one of the treatment types as described above; and (v) no treatment. For analyses, a binary variable that indicated whether the child was treated or not treated was created by combining the first four treatment groups.

Age at the time each follow-up questionnaire was returned was coded into four categories: younger than 7 years, 8 to younger than 13 years, 13 to younger than 18 years, and 18 years and older. Genotype of *MECP2* was categorized as p.R168X, p.T158M, p.R294X, p.R270X, p.R255X, p.R133C, p.R306C, p.R106W, C-terminal deletions (CT), early truncating (ET), large deletions (LD) and other miscellaneous mutations (other).

Statistical analysis

Generalized estimating equations (GEE) (Zeger and Liang, 1986), a generalized linear model that accounts for

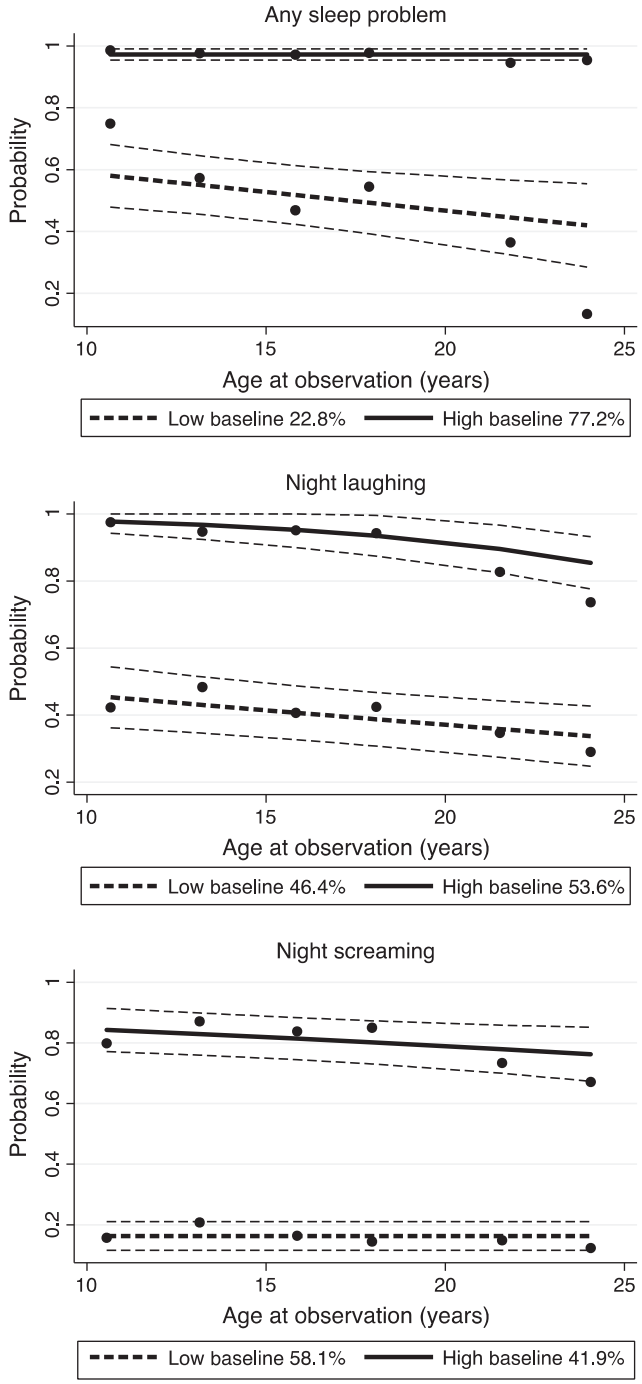

Figure 3. Trajectory of any sleep problem, night laughing and night screaming by latent class and age at observation. Low and high baseline represents the relative estimated level of prevalence of sleep problem at the first observation period in each group.

within-subject correlation of responses on dependent variables, was used to estimate the occurrence of any sleep problem and specific sleep problems as binary variables for the explanatory variables age group and mutation type, with the latter adjusted for age. Logit link function, robust standard errors and exchangeable working correlation structures were used for parameter estimation. Fitted probabilities of sleep problems for each explanatory variable were then estimated based on the recycled predictions approach using the Stata *margins* command.

Using the log link function, the GEE model was applied to ascertain the effect (risk ratio) of treatment at one time point on unresolved sleep problems at subsequent time points. Relative risk (RR) adjusted for age for each of the six time points was also obtained using log binomial regression analysis.

Latent class growth analysis (Nagin, 2005), a discrete mixture model of longitudinal data grouping, was used to identify developmental trajectories of any sleep problem and specific sleep problems (except night waking, as limited observations were available) as a continuous function of age. Temporal sequence of observation used in the analysis started from the first questionnaire returned. The number and shape of the sleep patterns was determined by selecting the model with a minimum value of Bayesian information criterion (BIC) (Andruff *et al.*, 2009), a criterion for model selection that ensures goodness-of-fit and penalizes over-fitting. The probability of belonging to specific trajectory group by mutation type was determined using logistic regression with group membership as the outcome variable and individual mutation type as the predicting variable.

Statistical analyses were conducted using STATA version 12 (StataCorp, 2011), SAS version 9.3 (SAS Institute Inc, 2002–2010) and both STATA and SAS versions of the command, traj (Jones and Nagin, 2007; Jones *et al.*, 2001; Nagin, 2005).

RESULTS

A total of 159, 189, 203, 208, 221 and 220 questionnaires were returned in 2000, 2002, 2004, 2006, 2009 and 2011, respectively. The median age at the first (2000) and last (2011) follow-up year was 13.0 years [interquartile range (IQR) 8.3–17.5] and 18.1 years (IQR 11.3–24.6) respectively. Over the six time points, the prevalence of any sleep problem was generally very high (>91%, except 85% in 2002) in the 7 years or younger age group and moderately high (73–98%) in the older age groups (Table 1). In those aged 18 years and above the condition appeared to be slightly less common in recent surveys. For night laughing, 60–88% of girls in the youngest age group experienced the problem and was more frequent in 2006 and 2009 when compared to other time points. Similar to that of any sleep problem, the prevalence of night laughing in the older age groups decreased in recent surveys. Night screaming, on average, was less common than night laughing, and for those in the 13–17 years age group the problem was reported less frequently over time (46% in 2000 versus 27% in 2011). Night waking was common, especially in the 7 years or younger age group. For those in the older age group (13 years or above), there was a decline in prevalence of this condition in recent questionnaire years. The prevalence of having both night waking and laughing ranged from 35% in 2011 to 55% in 2006. Similarly, for night waking and screaming, the prevalence was 26% in

2011 and 36% in 2006. The frequency and prevalence of specific sleep problems by occurrence frequency and year of questionnaire are shown in Table 2.

Age group

Taking into account of repeated data from each case, the estimated probability of any sleep problem was highest in the 7 years or younger age group (93%) and decreased with age (18 years and older: 82%) (Fig. 1). Night laughing was more common in the 7 years or younger (77%) and 13–17 years (74%) age groups than the older age groups. Prevalence of night screaming was higher in the youngest age group (49%) and was between 41 and 43% in other age groups. Night waking was common (75–80%), and the likelihoods were similar across the four age groups. The probability of persistent night laughing, screaming and waking also diminished with age.

Mutation type

The frequency distribution of mutation type by questionnaire year is shown in Table 3. After adjusting for age, the highest probabilities of any sleep problem were for those with a large deletion (94%), p.R270X (92%) and p.R294X (91%) mutations (Fig. 2). The presence of night laughing was reported for a high proportion of those with a large deletion (90%) and p.R168X (78%) mutation, while persistent night laughing was moderately common in those with p.R106W (49%) and p.R168X (42%) mutations. The highest probability of night screaming was estimated for those with p.R270X (57%), p.R306C (51%) and large deletion (51%) mutations. Interestingly, the likelihoods of night waking were lowest for early truncating (62%), p.R168X (75%) and p.R306C (75%). Similarly, persistent night waking was least likely in those with early truncating (50%), p.R306C (57%) and C-terminal deletions (58%) mutations.

Latent class growth analysis

Two distinct developmental trajectories were found for the presence of any sleep problem, night laughing and night screaming, and the probability of these sleep problems was estimated as a linear function of age. The two trajectories were labeled as 'high baseline' and 'low baseline', reflecting the relative estimated level of prevalence of sleep problem at the first observation period in each group.

In 77% of individuals with high baseline prevalence, a sleep problem tended to persist into adulthood. In contrast, a smaller group (23%), with a low prevalence when first observed, appeared to improve throughout the course of follow-up (Fig. 3). For night laughing and night screaming, the distributions in the two trajectory groups were more similar (night laughing 57% high versus 43% low prevalence group; night screaming 42% high versus 58% low prevalence group). In contrast, those who had a high prevalence of night laughing or screaming when younger improved with time, while for their low prevalence counterparts the problem persisted when they grew older.

Mutation types, as time-invariant covariates, were tested for their predictability of any and specific sleep problems. The model indicated that the presence of any *MECP2* mutation, in general, was more likely in those individuals with high baseline prevalence of any sleep problem compared with no *MECP2* mutation [odds ratio (OR): 2.65; 95% confidence interval (CI): 1.30–5.41]. Some mutation types, notably large deletion, p.R168X and p.R270X, were more common in the high baseline prevalence group of individuals with night laughing and night screaming, although the differences between groups were not significant (Fig. 4).

Treatment

The prevalence of receiving any treatment for sleep problems across the six time points was, on average, 16.1%. In terms

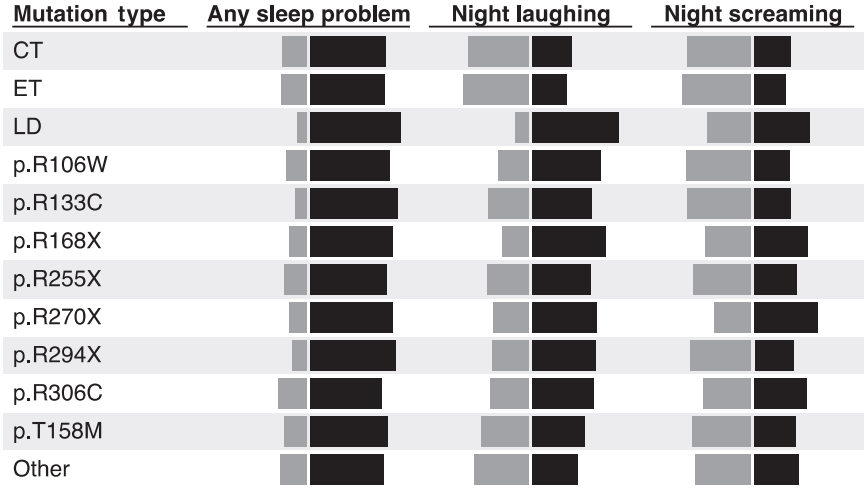

Figure 4. Predicted group membership probability by mutation type. Length of the horizontal bar represents the likelihood of sleep problems in girls and women with specific mutation type. CT, C-terminal deletions; ET, Early truncating; LD, Large deletion.

Table 4 Frequency and prevalence of sleep medication use in girls and women with a sleep problem by medication type and questionnaire year

	*Year of questionnaire [*n *(%)]*						
Medication	*2000 (*n *= 147)*	*2002 (*n *= 166)*	*2004 (*n *= 172)*	*2006 (*n *= 178)*	*2009 (*n *= 188)*	*2011 (*n *= 172)*	*Total*
Melatonin	1 (0.7)	2 (1.2)	3 (1.7)	6 (3.4)	10 (5.3)	9 (5.2)	31 (3.0)
Anti-epileptic drug	11 (7.5)	5 (3.0)	1 (0.6)	2 (1.1)	1 (0.5)	2 (1.2)	22 (2.2)
Benzodiazepine*	3 (2.0)	3 (1.8)	3 (1.7)	4 (2.3)	2 (1.1)	4 (2.3)	19 (1.9)
Benzodiazepine†	3 (2.0)	3 (1.8)	1 (0.6)	4 (2.3)	3 (1.6)	4 (2.3)	18 (1.8)
Clonidine	0	2 (1.2)	2 (1.2)	5 (2.8)	4 (2.1)	4 (2.3)	17 (1.7)
Trimeprazine	1 (0.7)	0	4 (2.3)	5 (2.8)	3 (1.6)	3 (1.7)	16 (1.6)
Amitriptyline	1 (0.7)	2 (1.2)	2 (1.2)	2 (1.1)	3 (1.6)	2 (1.2)	12 (1.2)
Risperidone	1 (0.7)	4 (2.4)	1 (0.6)	3 (1.7)	1 (0.5)	0	10 (1.0)
Promethazine	2 (1.4)	0	3 (1.7)	1 (0.6)	0	1 (0.6)	7 (0.7)
Miscellaneous	2 (1.4)	0	1 (0.6)	0	1 (0.5)	2 (1.2)	6 (0.6)
Olanzapine	0	1 (0.6)	0	1 (0.6)	1 (0.5)	2 (1.2)	5 (0.5)
Chloral hydrate	0	1 (0.6)	1 (0.6)	2 (1.1)	0	1 (0.6)	5 (0.5)
Haloperidol	0	1 (0.6)	0	0	1 (0.5)	1 (0.6)	3 (0.3)
Hypnotics	2 (1.4)	0	0	0	1 (0.5)	0	3 (0.3)
Mirtazapine	0	0	1 (0.6)	0	0	0	1 (0.6)
Fluoxetine	0	1 (0.6)	0	0	0	0	1 (0.6)

*Clobazam, clonazepam and diazepam.
†Nitrazepam, lorazepam, temazepam and oxazepam.

of treatment type, non-specific sleep medications were most commonly used (43.4%), followed by sleep medications (28.3%), multiple treatment types (16.4%) and non-pharmaceutical treatments (12.0%). The most commonly used medication was melatonin, which accounted for 17.6% of the responses (Table 4). Anti-epileptic medications and variants of benzodiazepine used for seizure control were used for sleep management in 12.5 and 10.8% of responses respectively.

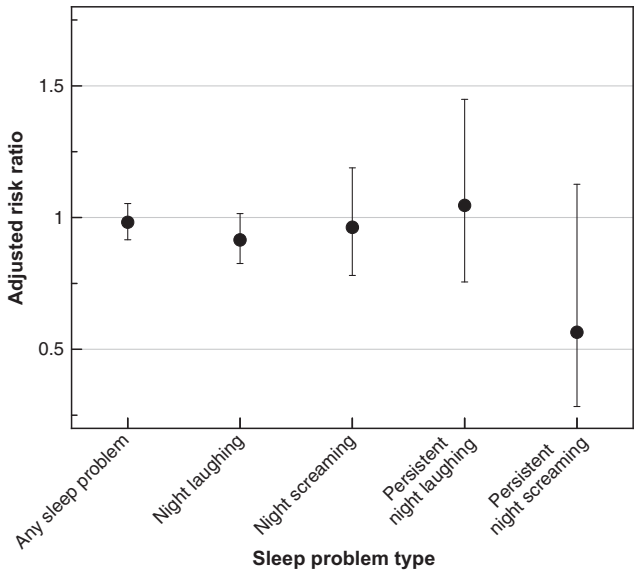

Figure 5. Effect of any treatment (compared to no treatment) on the likelihood of unresolved sleep problem by sleep problem type.

Treatment, on average, reduced the risk of any sleep problem from one time point to the next by approximately 1.7% (RR: 0.98; 95% CI: 0.92, 1.05) (Fig. 5). By questionnaire year, the effect was highest in 2000 (RR: 0.94; 95% CI: 0.80, 1.11) and 2002 (RR: 0.92; 95% CI: 0.76, 1.11) but shifted gradually to the null, and in 2009 treatment was associated with a small increase in risk (RR: 1.06; 95% CI: 0.92, 1.22) of sleep problems (Fig. 6). For night laughing and screaming, treatment has little effect on resolving the problems, but the risk of experiencing persistent night screaming appeared to be reduced (RR: 0.56; 95% CI: 0.28, 1.13). No obvious pattern was observed for the risks of night laughing and screaming.

For individuals who were treated with medications that were used specifically for sleep problems, including melatonin, the likelihood of any sleep problem persisting to a subsequent time point increased slightly (RR: 1.05; 95% CI: 0.97, 1.14) when compared with those who did not receive treatment for their sleep problem (Fig. 7). Specific sleep medications also appeared to reduce the risk of further night laughing and persistent night screaming, but not the occurrence of night screaming.

DISCUSSION

To our knowledge, this is the first study to examine the trajectory of sleep problems in Rett syndrome, using the largest population-based sample to date. The majority experienced sleep problems and the prevalence reduced slightly with age, in particular night screaming. There was some effect of *MECP2* mutation type: night laughing and screaming were common in those with a large deletion and

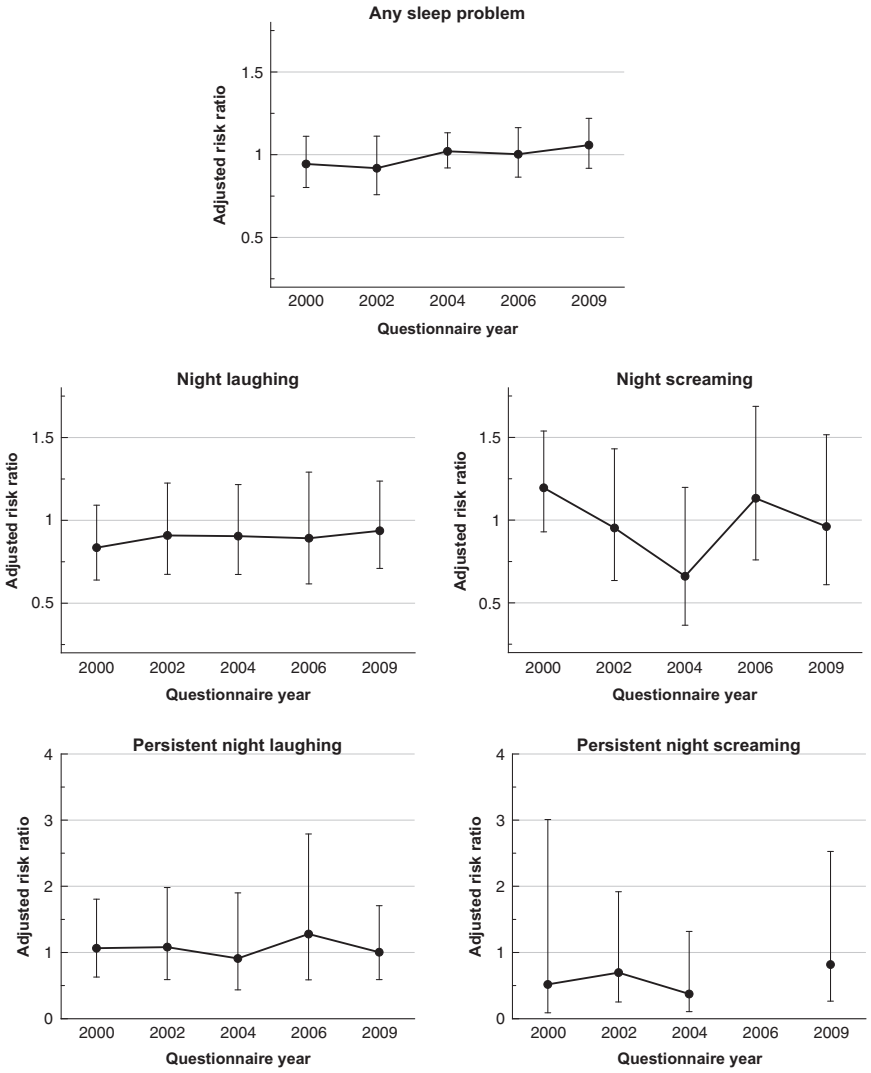

Figure 6. Effect of any treatment (compared to no treatment) on unresolved sleep problems by sleep problem type and questionnaire year.

night waking was less frequent for those with p.R306C, early truncating and C-terminal deletion mutations. By examining individual trajectories in response to treatment we were unable to identify any benefit. Latent class analyses indicated two longitudinal trajectories for sleep problems and membership with each group was not related to mutation type.

The prevalence of sleep problems in Rett syndrome was high (>80%), consistent with our previous population-based findings (Young *et al*., 2007). Parents reported that approximately three-quarters experienced night laughing and 40% screaming. Other than a case series undertaken almost three decades ago (Naidu *et al*., 1986) there is limited literature on the prevalence of sleep problems in Rett syndrome, and therefore the Australian longitudinal population-based source has proved to be a particularly valuable resource in this respect (Young *et al*., 2007). Sleep dysfunction occurs in other populations with intellectual disability (Didden *et al*., 2002) and autism (Wiggs and Stores, 2004), but may be particularly common in genetically caused syndromes associated with intellectual disability, e.g. Sanfilippo and Angelman syndromes (Dorris *et al*., 2008). A qualitative study of nine families with a daughter with Rett syndrome found that poor sleep affected the mood, energy levels and general performance of both the child and parents, with additional impact on parental relationships and social activities (Mcdougall *et al*., 2005).

Sleep problems in Rett syndrome may develop before or around the period of regression (Lee *et al*., 2013; Nomura, 2005), a time when the hallmark signs of Rett syndrome become apparent, often also accompanied by autistic signs such as social withdrawal and inconsolable crying (Lee *et al*., 2013; Nomura and Segawa, 1990; Witt-Engerström, 1993). We have reported previously that the prevalence of sleep problems was higher during childhood and slightly lower in adulthood (Young *et al*., 2007). Using trajectory and analyses population data now collected over 20 years, we have demonstrated in the present study that reduction in any of the symptoms of sleep dysfunction with time occurs in only a proportion of individuals. However, it was difficult to predict what factors were associated with this improvement. Whereas some symptoms decrease with age for some, the burden of sleep dysfunction continues for many girls and their families.

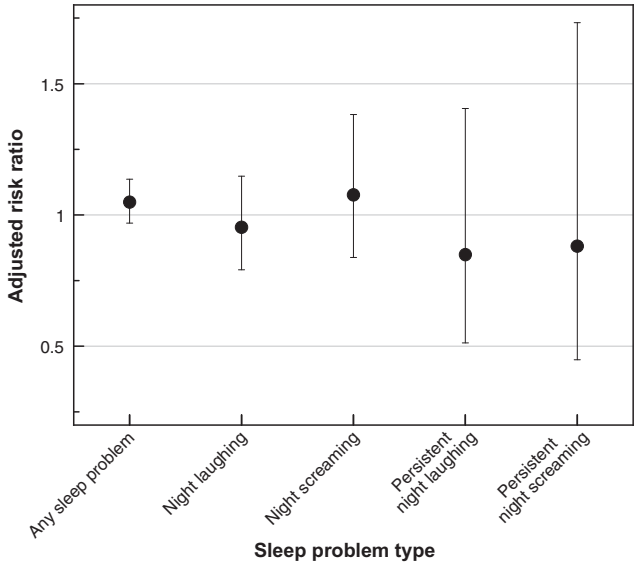

Figure 7. Effect of specific sleep medication (compared to no treatment) on the likelihood of unresolved sleep problem by sleep problem type.

The type of *MECP2* mutation has been associated with many aspects of the clinical phenotype in Rett syndrome, including early development (Fehr *et al*., 2011), clinical severity (Bebbington *et al*., 2008) and the prevalence of comorbidities such as epilepsy (Bao *et al*., 2013) and scoliosis (Ager *et al*., 2006). Sleep dysfunction occurred very commonly and, overall, we did not identify relationships with type of *MECP2* mutation. However, we found that there were some associations between specific aspects of sleep dysfunction and the type of mutation. For example, night laughing was reported more commonly for those with a large deletion and was more frequent in those with the p.R106W mutation, and night screaming was more likely in those with the p.R270X mutation. Conversely, persistent night waking was less common with the p.R306C, early truncating or C-terminal deletion mutations. We have now updated the findings of our previous study (Young *et al*., 2007), as our cohort has increased in size and followed over a longer period. Our more powerful analyses suggest that mutation has some role to play in the types of sleep dysfunction which, individually, may well be working through different mechanisms. Thus, investigations of the biology of sleep dysfunction in Rett syndrome should be cognizant of potential for the phenotype 'sleep dysfunction' to be heterogeneous in its underlying pathological mechanisms.

Managing sleep disturbance in Rett syndrome could potentially benefit both the child and the family, and available treatments include attention to sleep hygiene, associated behavioural strategies (Piazza *et al*., 1991), use of specific sleep medications such as melatonin (Mcarthur and Budden, 1998; Nomura *et al*., 1985) and chloryl hydrate, and the use of non-specific sleep medications such as anti-epileptic drugs, risperidone and haloperidol. The evidence base for treatment in Rett syndrome is extremely limited, and we were only able to identify three small studies investigating behavioural strategies (Piazza *et al*., 1991) or use of melatonin (or related) medications (Mcarthur and Budden, 1998; Nomura *et al*., 1985). Effectiveness in each study was limited to shorter time to sleep onset, but night waking persisted and there was decreasing effectiveness of melatonin with time (Mcarthur and Budden, 1998). Melatonin remains the most assessed sleep medication overall if one takes account of other literatures on treating sleep dysfunction for developmental disabilities (Hollway and Aman, 2011). With a limited body of evidence on how to manage sleep dysfunction in Rett syndrome and few demonstrated benefits, clinicians can only be guided by previous experience, anecdote and trial and error. The Australian experience would suggest a heterogeneous approach to management, with melatonin being used only in fewer than 5% of cases and little overall evidence of benefit to the patient of the approaches being used over more than a decade of observations. While sleep problems persisted overall, despite treatment, there was a reduced relative risk of persistent night screaming indicating that, for some, the severity of this aspect of sleep was reduced. However, the results from this study in combination with the lack of existing literature illustrate that the optimal types of management best suited to Rett syndrome are not yet known.

The Australian Rett Syndrome Database is population-based and longitudinal and has achieved high response fractions over its lifetime (Downs *et al*., 2008). Thus, it is a valuable and comprehensive resource for tracking symptoms in Rett syndrome. Our current study has investigated prevalence over time in the largest sample to date, and we have also been able to explore the effectiveness of treatments using a cohort study design. Over time, the questions on sleep dysfunction have been slightly modified and improved, making some adjustment or compensatory mechanisms necessary when comparing data from different waves. For instance, we referred to responses to the Rett Syndrome Behaviour Questionnaire (Mount *et al*., 2002) to determine the prevalence of night waking prior to 2009.

We acknowledge that our data set does not provide specific information on additional sleep disorders such as persistence of daytime napping (Ellaway *et al*., 2001), night-time seizures (Mcdougall *et al*., 2005), sleep-disordered breathing such as apnea and bruxism, which also have implications for health and wellbeing. Missing data are problematic in many studies. Those in this study with incomplete responses may not have had sleep problems and thus it is possible that we have overestimated the prevalence. We also acknowledge that our assessment of treatment effectiveness has limitations, including the broadness of our data in terms of the ordinal scale and the biennial observations. However, our analyses provide important new information in an area that is lacking and have the advantage of a 12-year lens through which to observe effects. We have identified a strong platform of need that strongly justifies research efforts to identify and test an effective treatment for sleep dysfunction in Rett syndrome.

Our study has important implications for clinicians. Sleep problems are extremely common in Rett syndrome, with a significant burden for the health and wellbeing of both those with Rett syndrome and their families. Clinical management is heterogeneous and does not appear to be associated with clear and consistent improvement. Therefore, clinicians can only be guided by their previous experience and careful assessment and follow-up in order to judge effectiveness on a case-by-case basis. The organization of access to respite options may be critically important for family health and wellbeing. There is an urgent need to understand the mechanisms of sleep dysfunction in Rett syndrome and thereafter identify and test treatments for its amelioration.

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AUTHOR CONTRIBUTIONS

KW, HL and JD conducted the study design; HL, CE and JD carried out the data collection; KW and PJ analysed the data; KW, HL, PJ, CE and JD interpreted the results; and KW, HL and JD prepared the manuscript.

CONFLICT OF INTEREST

No conflicts of interest declared.

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