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Sleep problems in individuals with Rett Syndrome: A systematic review and meta-analysis

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ABSTRACT

Importance: Prognosis and understanding of sleep disorders in rare genetic syndromes is limited, despite being a common complaint of caregivers. Rett Syndrome (RTT) is a rare, progressive neurodevelopmental disorder with problematic sleeping being a clinical feature yet inconsistencies exist in the literature.
Objective: To examine the strength of evidence of a sleep disorder in RTT. To investigate the complaints reported based on a sleep disorders classification approach and to determine differences in rates per the RTT main clinical features.
Data sources: PubMed, Web of Science, PsycINFO, Ebsco, Scopus, and Cochrane Library up to November 4th 2021 with no time or language limitation (CRD 42020198099) were searched.
Study selection: Original research published in peer-reviewed journals, with RTT clinical or genetic diagnosis reported and stating a sleep complaint with prevalence rate, were selected.
Data Extraction and Synthesis: We followed the PRISMA guideline for abstracting data and assessed risk of bias with the NIH quality assessment tools. The prevalence rates were meta-analyzed applying the mixed-effects model with measures of consistency.
Main Outcome(s) and Measure(s): The International Classification of Sleep Disorders was used to summarize sleep complaints reported in the literature. Those that did not specify the precise sleep complaint were categorized as a not otherwise specified sleep problem. We further analyzed data per available RTT characteristics.
Results: We included 19 studies (n = 4298, 0.3 to 57.2 years old) across five countries involving predominantly observational study designs. Overall, 54.1% (95%CI: 43.8% to 64.5%) of individuals with RTT exhibit problematic sleeping, in particular, excessive somnolence (67.5%; 95%CI: 47.5% to 82.7%) and difficulties initiating and maintaining sleep (61%; 95%CI: 49.6% to 71.4%). Disturbed sleep not otherwise specified was reported in 57.1% (95%CI: 34.5% to 81.3%). Although studies could improve details reported, females with *MECP2*-RTT showed a higher prevalence rate of excessive somnolence and sleep-wake transition disorders than those diagnosed by *CDKL5*-RTT. **P**revalence rates remain roughly unaltered across the lifespan. Sleep disorders are about two times more prevalent than in typically developing children.
Conclusions and Relevance: Findings indicate predominantly disorders regarding maintenance of sleep and wake state, which persist throughout their lifespan. Improved reporting of clinical features in cases with RTT phenotypes and of sleep behavior frequency and severity may lead to explicit prevalence rates. This is fundamental to progress in the pathophysiological investigation of altered sleep-wake mechanisms and to implement tailored sleep interventions for individuals with RTT, and families.

Introduction

Rett Syndrome (RTT, OMIM #312750) is a severe, rare neurodevelopmental disorder [1] and the second common cause of genetic multidisabilities [2] with an approximate incidence of 1/10,000 female births [3,4]. Six to eighteen months after birth, a regression of acquired spoken language and purposeful hand skills, with emergence of hand stereotypies and gait abnormalities [5,6] characterizes typical RTT. Some individuals present clinical characteristics that vary subtly, and hence are identified as suffering an atypical variant of RTT [7,8]. Mutations in gene encoding Methyl-CpG-binding protein 2 (*MECP2*) located in the Xq28 region [9] are involved in the majority of RTT cases (96%) [10]. Several atypical variants might be explained by cyclin dependent kinase like 5 (*CDKL5*) and forkhead box G 1 (*FOXG1*) [11,12]. These genetic causes may share a common molecular pathway involved in gene transcription modulation [13,14], affecting brain growth and maturation [15].

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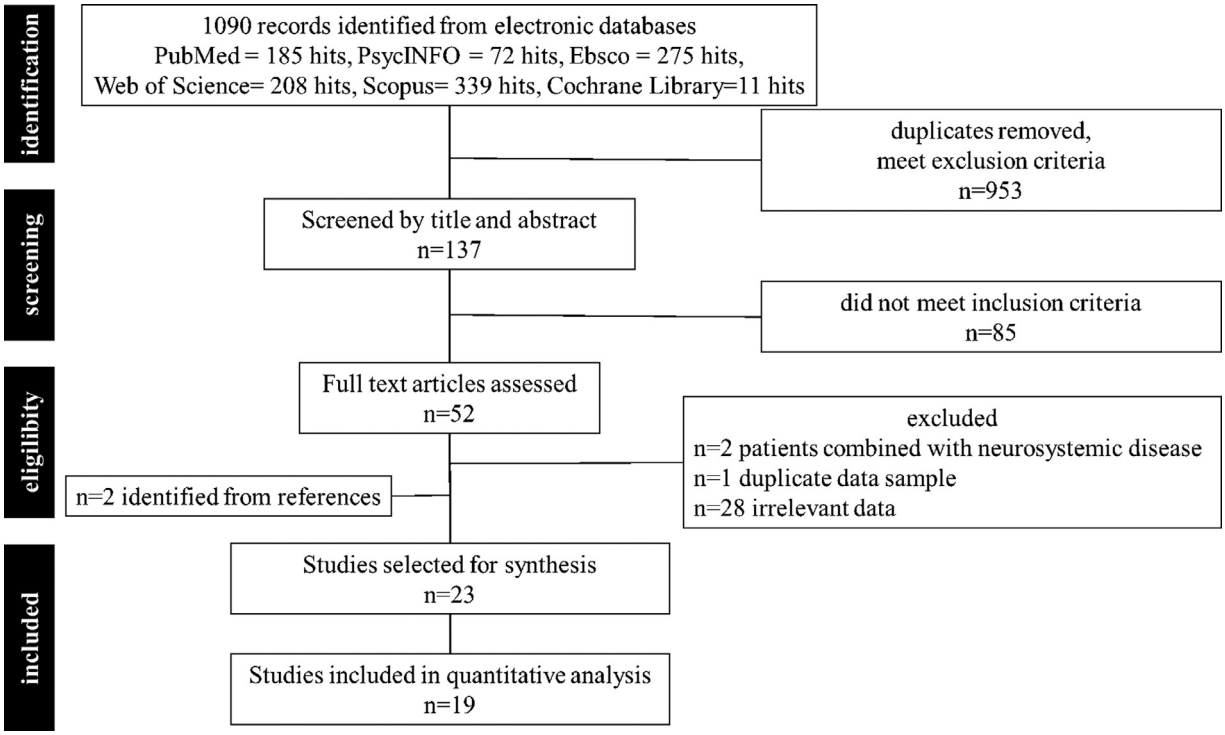

Fig. 1. Flowchart of article selection (November 24th 2021).

Sleep is tightly associated to the overall development of a child, [16] and has an important function of synaptic homeostasis in brain plasticity processes [17]. Sleep problems are moreover reported to be highly prevalent in RTT samples [18–21], e.g., over 80% [22–25], but discrepancies exist in the literature (for example reports of nightwaking range from 33% to 93%). In the absence of any systematic review on this syndrome, a meta-analysis was conducted to advance our understanding of differences in reported prevalence rates with respect to clinical characteristics. Alternatively, such phenotyping may facilitate new venues for clinical interventions and pathophysiological research in RTT.

Methods

This meta-review applied the PRISMA 2009 reporting guidelines [26] and was registered in PROSPERO (CRD 42020198099).

Search strategy and selection criteria

KS and XYZ screened and selected sleep studies on RTT individuals form PubMed, Web of Science, PsycINFO, Ebsco, Scopus, and Cochrane Library to November 24th 2021 (**Fig. 1**) with the search terms: "Sleep AND Rett Syndrome" (see **eTable. 1**).

Studies were eligible upon fulfilling the following criteria: 1) original research published in peer-reviewed journals; 2) RTT clinical or genetic diagnosis reported; 3) a sleep complaint with prevalence rate (PR) stated.

No time limitations or study design restrictions were applied. Studies are excluded if participants were RTT individuals with other central nervous system complications (e.g., neurofibroma). Animal studies are reported elsewhere [27].

Data collection and analysis

Study information, sample characteristics, and sleep-related data were extracted.

Sleep complaints were sorted into subscales fitting the International Classification of Sleep Disorder (ICSD) [28,29] into problems related to: disorders of initiating and maintaining sleep (DIMS), sleep–wake transition disorders (SWTD), daytime excessive somnolence (DES), and disorders of arousal during sleep (DA).

For the studies that did not specify the precise sleep complaint, it was labelled as "disturbed sleep". This approach was similarly applied to studies reporting the number of individuals at or above "a sleep problem cutoff score", given the sleep questionnaire used, in the absence of more detailed information. Both were categorized into a subscale "not otherwise specified (NOS) sleep problems".

Next, we pursued a meta-review per available RTT characteristics: age (i.e., per the age category of PubMed), gender (i.e., female and male), gene (i.e., *MECP2, CDKL5* and *FOXG1*) and clinical classification [6] (i.e., typical and atypical).

Statistical analysis

Statistical analysis were conducted with Statistica TIBCO Software Inc (TIBCO, 2017) version 13 and Meta-analysis with Comprehensive Meta-Analysis version 3.3.070 (Biostat, Englewood, NJ). The heterogeneity between studies is described by I^2 (i.e., I^2=0: no, $0 < I^2 \leq 25\%$: low, $25\% < I^2 \leq 75\%$: moderate, $I^2 > 75\%$: high heterogeneity). Tau-squared is the variance of the effect size parameters across the population of studies. The mixed effects model was chosen to estimate the pooled (prevalence rate, PR) and illustrated by forest plots with the 95% confidence intervals (95%CI). The z-value and *p-value* indicate whether the effect size is significantly different from zero. That is, in meta-analysis the null hypothesis is that all of the separate null hypotheses are true. To test the robustness of our findings an Egger's test was applied for assessing risk of bias.

Quality assessment of studies

Each study was scored per the Study Quality Assessment Tools of the National Institutes of Health [30] applicable to several study designs. We

Table 1
The selected articles.

Author (Year)	Country	Gender (n)	Age (yrs) mean±SD[range]	Clinical RTT diagnosis (n)	Diagnose Specifics (n)	Diagnostic criteria	Sleep assessment tool	ICSD scale	Data Source	Time of data collection	Type of Study	NIH quality assessment
Peron et al. (2020) [45]*	Italy	Female (54)	[19–49]	TYPICAL(47) ATYPICAL(4) TYPICAL without genetic diagnosis (3)	MECP2 (43): ESV (3), PSV (1), no pathogenic variant (2); FOXG1 (2); CDKL5 (2); no testing (1)	Neul [6]	Clinical profile	NOS, DIMS	Multidisciplinary Rett clinic, San Paolo University Hospital, Italy, since 2006	last medical visit 01/2018–12/2019	observational, cross-sectional, retrospective study	Poor
	Genetic etiology (n): ***MECP2*** (47); ***CDKL5*** (2): NM_001323289.2 [c.1648C>T; p.(Arg550Ter AND c.607G>C; p.(Glu203Gln)]; ***FOXG1*** (2): NM_005249.3 [c.256delC;p.(Gln86ArgfsX106) AND 2 Mb 14q12deletion (28 780 663–30 780 833; hg19), de novo]											
Leven et al. (2020) [40]*	United Kingdom	Female (286) Male (1)	0–6: 55 7–12: 54 13–18: 51 >18:127	TYPICAL (287)			Sleeping Questionnaire for Children with Neurological and other Complex Diseases (SNAKE)	NOS	Rett Aid or Elternhilfe für Kinder mit Rett-Syndrom in Deutschland e.V	09/2017–12/2017	observational, cross-sectional, prospective study	Poor
	Genetic etiology (n): No information											
Frullanti et al. (2019) [32]*	Italy	Unknown:1007 (twins included)	>5	TYPICAL (806) ATYPICAL (201)	MECP2 (949): classic (804), CV (24), ESV (5), PSV (54), atypical (62) CDKL5 (32): ESV (31), atypical (1) FOXG1 (26): CV (22), classic (2), atypical (2)	Ariani [48], Guerrini [56]	Clinical profile	NOS	Rett Networked Database (RND), a registry of 13 European countries https://www.rettdatabasenetwork.org	03/2017	observational, cross-sectional, retrospective study	Poor
	Genetic etiology (n): ***MECP2*** (949): C-Term (101), Early truncation (93), Large deletion (72), p.R106W (31), p.R133C (62), p.T158M (102), p.R168X (80), p.R255X (106), p.R270X (62), p.R294X (63), p.R306C (67), other (110); ***CDKL5*** (32): Early truncation (7), Late truncation (9), Missense mutation (10), Large deletion (6); ***FOXG1*** (26)											
Merbler et al. (2018)[51]*	United States of America	Female (9)	9.4 ± 4.2 [1.7–17.1]	TYPICAL (7), ATYPICAL (2)	MECP2 (8) *MECP2*-related disorder (1)		CSHQ	NOS	Local parent support network in the Midwest of United States of America		observational, cross-sectional, prospective study	Good
	Genetic etiology (n): ***MECP2*** (9): p.P152R (1), p.R168X (2), p.R255X (1), p.R106W (1), p.A131fs (1), Exon 4 deletion (1), Deletion between exon 3 and 4 (1), p.K144X (1)											
Mori et al. (2018) [25]	Australia	unknown In 2002: 132 In 2006: 140 In 2009: 168 In 2011: 160	All		MECP2 (140); other (19); no pathogenic variant (39)	Trevathan and Moser [57] (applicable for age 2–5yrs) + Hagberg and Skjeldal [8]	Rett Syndrome Behaviour Questionnaire	NOS	Australian Rett Syndrome Database (ARSD), registry since 1993	2002 2006 2009 2011	observational, cohort, retrospective study	Good

(*continued on next page*)

Table 1 (*continued*)

	Genetic etiology (n): *MECP2* (140): C-Term (20), Early truncation (11), Large deletion (12), p.T158M (18), p.R168X (13), p.R294X (12), p.R270X (11), p.R255X (10), p.R133C (17), p.R306C (9), p.R106W (7)											
Mori et al. (2017) [58]	Australia	ARSD: Female (184) ICDD: *Female (143); Male (25)*	ARSD: [2.6–35.7] ICDD: [0 –34.7]	RTT (184)	CDKL5 (164)		a frequency of night waking over the previous 2 years, a customized question from SDSC	DIMS	Australian Rett Syndrome Database (ARSD), registry since 1993 International *CDKL5* Disorder Database (ICDD), since 2012	ARSD: 2011 ICDD: 11/2012–04/2016	observational, cohort, retrospective study	Good
	Genetic etiology (n): No information											
Boban et al. (2016) [37]*	Australia	Female (362) Male (2)	[2.1–57.2] 0–7: 56; 8–12: 106; 13–17: 92; >18: 110		MECP2 (321) Other (43)	Neul [6]	SDSC	DIMS, SWTD, DES, DA	InterRett, since 2002; survey of UK, USA, Canada and Australia English speaking families		observational, cross-sectional, prospective study	Good
	Genetic etiology (n): *MECP2* (321): C-Term (40), Early truncation (23), Large deletion (25), p.T158M (36), p.R168X (39), p.R294X (27), p.R270X (23), p.R255X (40), p.R133C (27), p.R306C (25), p.R106W (16)											
Mangatt et al. (2016) [49]*	Australia	*MECP2: female (321) CDKL5: Female (143); Male (24)*	*MECP2*: [2–35.5] *CDKL5*: [0.3–29.1]		MECP2 CDKL5 (151)		SDSC	DIMS, SWTD, DES, DA	ICDD (http://cdkl5.childhealthresearch.org.au). ARSD, InterRett to complete missing data	*MECP2*: 2000, 2002, 2004, 2006, 2006, 20,111 *CDKL5*: 06/2015	observational, cohort, retrospective study	Poor
	Genetic etiology (n): *MECP2* (321); ***CDKL5*** (164): No functional protein(51), Missense/in-frame mutation within catalytic domain (45), Truncation between aa172 and aa781 (38), Truncation after aa781 (17), Mutation not grouped (13)											
Pini et al. (2016) [59]*	Italy	Female (149) Male (2)	12 [1–49]	CLASSIC (**98**) ATYPICAL (53)	MECP2 (118) : PSV (19) [MECP2+ (18) & MECP2- (1)], ESV (13) [*CDKL5 (12) &] CDKL5-e MECP2- (1)]*, CV (1) [*FOXG1 (1)] ;* ARTT-NOS (19) [MECP2+ MALE (2) , MECP2+ (18), MECP2- (13) , MEF2C (1))	Neul [6]	Clinical severity score	NOS	Tuscany Rett Center, Versilia Hospital	01/2006–04/2014	observational, cross-sectional, retrospective study	Poor
	Genetic etiology (n): No information											
Ammanuel et al. (2015) [39]*	United States of America	Female (10)	6.2 ± 0.7 [2–9]		MECP2 (10)		Clinical severity score	NOS	convenience sample		observational, cross-sectional, retrospective study	Good

(*continued on next page*)

Table 1 (*continued*)

	Genetic etiology (n): *MECP2* (10): p.T158M (1), p.R168X(P) (1), p.R294X (1), p.R270X (1), p.R133C (3), p.R106C (1), p.D134C (1), 1085del_1197del (1)										
Cianfaglione et al. (2015) [60]*	United Kingdom	Female (91)	20.5 [4–47]	CLASSIC(69), ATYPICAL(19), *MECP2*-related disorder (3)	MECP2 (71) No mutation (20)	Hagberg [61] Neul [6]	Non-communicating children's pain checklist including Sleeping	NOS	British Isle Rett Syndrome Survey (BIRSS), since 1982		observational, cross-sectional, prospective study	Poor
	Genetic etiology (n): *MECP2* (71): C-Term (13), Early truncating (26), Late truncating (7), Large deletion (2), PIANMissense (23)										
Wong et al.(2015) [22]*	Australia	Females (320) In 2000: 159 In 2002: 189 In 2004: 203 In 2006: 208 In 2009: 221 In 2011: 220	[2–35.8]		MECP2	Neul [6]	Mixture of clinical severity items and Rett Syndrome Behavior Questionnaire	NOS, DIMS, DA	ARSD	2000; 2002; 2004; 2006; 2009; 2011	observational, cohort, retrospective study	Poor
	Genetic etiology (n): In 2000: ***MECP2*** (118): C-Term (12), Early truncation (7), Large deletion (5), p.T158M (14), p.R168X (15), p.R294X (10), p.R270X (12), p.R255X (8), p.R133C (8), p.R306C (7), p.R106W (3), Other (17), No mutation (33); In 2002: ***MECP2*** (137): C-Term (12), Early truncation (10), Large deletion (8), p.T158M (16), p.R168X (16), p.R294X (12), p.R270X (14), p.R255X (8), p.R133C (10), p.R306C (9), p.R106W (2), Other (20), No mutation (44); In 2004: ***MECP2*** (154): C-Term (15), Early truncation (8), Large deletion (10), p.T158M (16), p.R168X (19), p.R294X (15), p.R270X (14), p.R255X (11), p.R133C (11), p.R306C (10), p.R106W (4), Other (21), No mutation (41); In 2006: ***MECP2*** (157): C-Term (17), Early truncation (7), Large deletion (11), p.T158M (17), p.R168X (15), p.R294X (15), p.R270X (13), p.R255X (11), p.R133C (11), p.R306C (11), p.R106W (7), Other (22), No mutation (43); In 2009: ***MECP2*** (171): C-Term (20), Early truncation (10), Large deletion (12), p.T158M (18), p.R168X (14), p.R294X (15), p.R270X (15), p.R255X (15), p.R133C (18), p.R306C (9), p.R106W (7), Other (18), No mutation (39); In 2011: ***MECP2*** (170): C-Term (18), Early truncation (10), Large deletion (12), p.T158M (20), p.R168X (17), p.R294X (13), p.R270X (14), p.R255X (12), p.R133C (18), p.R306C (10), p.R106W (9), Other (17), No mutation (36)									
Anderson et al. (2014) [44]	Australia	Females (391) ARSD: 142, InterRett: 249	[18–54]		MEPC2 (171) Other (62)	Neul [6], Hagberg [61], The Rett Syndrome Diagnostic Criteria Work Group [62]	Items from clinical severity	NOS, DA	ARSD, InterRett, since 2002	01/2014	observational, cohort, retrospective study	Poor
	Genetic etiology (n): *ARSD* ***MECP2*** (111): C-Term (11), Early truncation (7), Large deletion (6), p.T158M (12), p.R168X (12), p.R294X (9), p.R270X (9), p.R255X (9), p.R133C (10), p.R306C (6), p.R106W (4), Other (16) Interrett MECP2 (122): C-Term (8), Early truncation (6), Large deletion (5), p.T158M (4), p.R168X (9), p.R294X (7), p.R270X (8), p.R255X (10), p.R133C (7), p.R306C (6), p.R106W (6), Other (46)											
Fehr et al.(2012) [38]	Australia	*CDKL5*: females (69), males (8) *MECP2*: females (920)	*MECP2*: 10.5 [1.3–54.2]; *CDKL5*: Females: 6.1 [0.5–22.4]; Males: 5.2 [1.−14.9]		ESV (19), CDKL5 (56)		clinical severity	NOS	InterRett, since 2002		observational, cross-sectional, retrospective study	Good
	Genetic etiology (n): *MECP2* (920)**; *CDKL5*** (86): Missense (26), Nonsense (16), Splice site (12), Insertion/deletion (21), Large deletion/duplication (10), Unknown (1)										
Hagebeuk et al.(a) (2012) [35]*	The Netherlands	Females (4)	6.5 ± 5.8 [2–15]	ATYPICAL(4)	CDKL5 (4)		SDSC	NOS/ DIMS, SWTD, DES, SDB	Convenience sample		Case series	Good
	Genetic etiology (n): *CDKL5* (4): c.656A>C (1), c.660_664dup (1), c.283–3_290del (1), c2635_2636del (1)										
Hagebeuk et al.(b) (2012) [34]*	The Netherlands	Females (8)	9.8 ± 8.1 [3–33]	III (6), IV (1)	MECP2 (6); UNKNOWN (2)	Hagberg [63]	SDSC	NOS	Convenience sample		Case series	Good
	Genetic etiology (n): *MECP2* (8)										
Vignoli et al. (2011) [64]*	Italy	Females (84)	24±6.7 [14–42]		MECP2 (59); CDKL5 (1); No mutation (16)		clinical severity; modified Kerr score [52]	NOS, DIMS	Italian Association for Rett Syndrome (AIR) who have children aged >14 years		observational, cross-sectional, prospective study	Poor

(*continued on next page*)

Table 1 (*continued*)

	Genetic etiology (n): ***CDKL5*** (1); ***MECP2*** (59): C-Term (8); p.R270X, p.R255X, 750insC (13); p.R294X (6). p. R168X, p.Y141X (5); p.R306C (5); p.T158M (4); Del exons 3 and 4 (3); p.R133C (3); p.P152R (2); p.P322A (1); p.R106W (1); p.P225R (1); p.T158A (1); p.A2V (1); Unknown, not specified (5)										
Halbach et al. (2008) [55]*	The Netherlands	Females (53)	26.9 ± 7.85 [16–53]	MECP2 (31); MECP2 negative (4); UNKNOWN (2);. NO TEST (12); UNKNOWN GENOTYPE (4)		Observational Questionnaire Elderly Residents with Intellectual Disabilities	DIMS, SWTD, DES, DA	Dutch RTT parent association		observational, cross-sectional, prospective study	Poor
	Genetic etiology (n): No information										
Young et al. (2007) [24]*	Australia	unclear (216) In 2000: 163 In 2002: 196 In 2004: 202	[2–29]	MECP2 (164), NO TEST (52)	Leonard [65], Hagberg [63]	clinical severity	NOS, SWTD, DA, DES	ARSD, registry since 1993	2000 2002 2004	observational, cohort, retrospective study	Good
	Genetic etiology (n): In 2000: ***MECP2*** (112): C-terminal deletion (14), Early truncating (8), Large deletion (5), p.R106W (3), p.R133C (6), p.R168X (15), p.R255X (8), p.R270X (12), p.R294X (9), p.R306C (7), p.T158M (14), Other (11), No mutation (34); In 2002: ***MECP2*** (131): C-terminal deletion (15), Early truncating (11), Large deletion (8), p.R106W (2), p.R133C (9), p.R168X (16), p.R255X (7), p.R270X (14), p.R294X (12), p.R306C (9), p.T158M (15), Other (13), No mutation (45): In 2004: ***MECP2*** (141): C-terminal deletion (17), Early truncating (10), Large deletion (8), p.R106W (4), p.R133C (10), p.R168X (18), p.R255X (10), p.R270X (13), p.R294X (15), p.R306C (9), p.T158M (14), Other (13), No mutation (42)										
Cooper et al. (1998) [66]*	United Kingdom	Females (125)	[2–60]	CLASSIC (125)	The Rett Syndrome Diagnostic Criteria Work Group [62]	clinical severity	NOS, DES	British Rett Survey	1987–1996	observational, cross-sectional, retrospective study	Poor
	Genetic etiology (n): No information										
Sansom et al. (1993) [67]*	United Kingdom	Females (107)	10.6 ± 5.4 [2.2–28] ≤5: 20 6–10:43 11–15:25 ≥16:19		confirmed by Professor Andreas Rett and/or Dr. Alison Kerr	clinical severity	NOS, DIMS, DA	National RTT Association of United Kingdom		observational, cross-sectional, prospective study	Poor
	Genetic etiology (n): No information										
Zappella et al. (1990) [33]*	Italy	Females (13)	8 ± 3.4 [3–14]	CLASSIC(12), FORME FRUSTE(1)	Hagberg [68]	parental report	DIMS	Convenience sample		before-after with no control study	Poor
	Genetic etiology (n): No information										
Coleman et al. (1988) [69]*	United States of America	Females (63)	7.3 ± 3.8 [2–20]		Physician criteria after visit Dr. A. Rett	clinical severity	NOS, DIMS	International RTT Association in United States of America and Canada, parent group, since 1985	01/1985–07/1985	observational, cross-sectional, retrospective study	Poor
	Genetic etiology (n): No information										

*Selected for meta-analysis. **AIR:** Italian Association for RTT; **ARTT-NOS:** Atypical RTT-not otherwise specified; **BIRSS:** British Isle RTT Survey; **C:** Clinical diagnosis; **CDD:** CDKL5 Deficiency Disorder; ***CDKL5*:** Cyclin dependent kinase-like 5; **CSHQ:** Children's Sleep Habit Questionnaire; **CV:** Congenital variant; **DA:** disorder of arousal; **DES:** disorder of excessive somnolence; **DIMS:** disorder of initiating and maintaining sleep; **ESV**: Early seizure onset variant; **F:** female; ***FOXG1*:** Forkhead box G1; **G:** Genetic test; **ICDD:** International *CDKL5* Disorder Database; **ICSD:** International Classification of Sleep Disorder scale; **M:** male; ***MECP2*:** Methyl CpG binding protein 2; ***MEF2C*:** Mads box transcription enhancer factor 2; **NOS:** non-specified otherwise; **PSV:** Preserved speech variant; **RND:** Rett Networked Database; **RTT:** Rett Syndrome; **SDB**: sleep-disordered breathing; **SDSC:** Sleep Disturbance Scale for Children; **SNAKE:** Sleeping Questionnaire for Children with Neurological and other Complex Diseases; **SWTD:** sleep–wake transition disorder.

followed the same approach as previously published. [31] Study quality is reported as: “study population, definition and selection”, “soundness of information”, “analysis, comparability and outcomes” and “interpretation and reporting” and evaluated as poor, fair and good.

Disagreement in selection, extraction and quality scoring was resolved by discussion.

Results

Study characteristics

Table. 1 contains the 23 papers selected for this meta-review (**Fig. 1**), and marked (asterisks) are the 19 papers usable for analyses.

Their publication date ranged from 1988 to 2020, and data reflect samples from 1985 to 2019, yet for ten papers this information was not available. Data from five research groups are included: 26.3% Italy, 21.1% for both United Kingdom and Australia, and 15.8% for both USA and Netherlands.

For two studies, we presumed female gender [24,32], while 13 studies reported only female data. In four studies separate data for males and females were reported ($n = 2$) or not ($n = 2$). The number of studies reporting data per age-groups are: 0–7 years = 10 studies, 8–12 years = 8 studies, 13–17 years = 9 studies and 18+ years = 9 studies. Information about the genotype was not always provided, resulting in 11 on *MECP2*, five studies on *CDKL5*, and three studies on *FOXG1*. Mutation types were reported in 11 studies but further analysis could not be pursued. Nine studies reported the type of clinical diagnosis. Most studies used diagnostic criteria by Neul ($n = 4$), but also Hagberg either or not combined ($n = 4$) and per Andreas Rett personally ($n = 2$), others were Ariani & Guerrini criteria and RTT clinical workgroup.

This meta-review represents a total sample size of 4298 (min. 2 to max. 926) with an age-range from 0.3 to 57.2 years old, and including 18 males. Data sources were from clinic ($n = 6$), Australian Rett Syndrome Database (ARSD, $n = 3$), InterRett ($n = 2$), others were: International *CDKL5* Disorder Database (ICDD), Rett Networked Database (RND), Rett Aid or Elternhilfe für Kinder mit Rett-Syndrom in Deutschland e.V, British Isle Rett Syndrome Survey, Italian Association for Rett Syndrome, British Rett Survey, and support groups ($n = 5$).

Studies were mostly observational designs ($n = 16$) with one study applying a before-after design without controls [33] and two studies being case series [34,35]. Data collection was retrospective in nine studies and seven studies applied a prospective data collection method. Two studies involved repeated assessments yet only one time point (i.e., 2009 [22], 2004 [24]) was chosen for analysis. Thirteen of the 19 studies showed poor quality. That is, quality assessment (**Table. 1** and **eFig. 1**) indicated that “study population, definition and selection” and “interpretation, reporting” were somewhat better reported, but “soundness of information” and “analysis, comparability and outcomes” should be improved. Egger regression coefficient (for more than two datasets, see Figures) was predominantly non-significant, indicating nearly no publication bias.

General information on the sleep problems

We will report findings grouped per ICSD subscales and its sleep item when available. A total of 20 sleep complaints were reported. Because several studies measured sleep items in terms of occurrence or severity, we harmonized them into “no” when absent and “yes” when present. “Yes”: reported as “sometimes”, “often”, “less than once a month”, “monthly”, “twice a month”, “once or more a week”, “nightly”, “more than once a night”, “bad”, “milder”, “moderate” and “severe”. “No”: reported as “did not occur”, “never”, “has stopped”, “very good”, “good”, “satisfying”, “not present” and “none”. Sleep behaviors mostly queried are belonging to DA and SWTD.

The largest analyzed sample size was for DA ($n = 1412$) next was, NOS ($n = 875$), DIMS ($n = 842$), SWTD ($n = 676$), DES ($n = 491$), and SBD ($n = 2$) (see Figures).

RTT samples

Fig. 2 shows the pooled PR per ICSD subscales in all females diagnosed with RTT. Per subscale, high heterogeneity and non-significant results demonstrate inconsistency in study findings. Significant sleep problems across the subscales are daytime somnolence (85%), nightly unrest (77%), terminal insomnia (74.8%), repetitive movements (27.1%), sleep talking (17.8%) and night terrors (17.8%) and, for those able to walk, sleep walking (4.4%). In 55.6% “a” sleep complaint (or NOS) was reported, yet with high heterogeneity.

Including the mixed gender samples, comparable subscale heterogeneity and non-significance was found. Separate sleep issues that are in addition significantly prevalent (**Fig. 2**) when including both genders were: difficulty falling asleep (60.3%), night screaming (34.6%), difficulty waking (31.1%) and only daytime sleep problems (15.2%).

Stratifying analyses per age-groups, for the subscales, in the 13–17 years old females a significant pooled PR for DIMS (74.8%, no heterogeneity) (**eFig. 2**) and in the 18+ years old females for DES (85.1%, no heterogeneity) were found. In each of the age-groups, night laughing (>60%) and when applicable also sleep walking was prevalent. Terminal insomnia is prevalent in all except 18+. Sleep complaints that were individually significant in each of the 8–18+ age-groups were night terror and sleep talking. While teeth grinding was only prevalent in the 0–7 years old. The age group 18+ had the largest number of significant sleep complaints.

Including the mixed gender samples per age-groups (**eFig. 3**), the DIMS subscale was significant in the 0–7 years old (73.3%, low heterogeneity) and in the 8–12 years old (74.7%, high heterogeneity). For 18+ years old the DES (similar to RTT females) and DA (27.7%, high heterogeneity) were characteristic. Night laughing and terminal insomnia were prevalent in all except 18+, and when applicable also sleep walking was prevalent in all. Night terror, night waking were prevalent in all except the 0–7 years old but in this age group difficulty falling asleep was significantly prevalent.

MECP2 samples

Including only female data with confirmed *MECP2* demonstrated a significant pooled PR for DES (79.6%, moderate heterogeneity), involving sleepy during daytime (85%) and napping (77.2%) (**eFigure 4**). Several other sleep complaints are significant (**eFigure 4**): night waking (81.9%), nightly unrest (77%), night laughing (66.3%), night screaming (40.1%), night terror and sleep talking (each 17.8%) and sleep walking (4.3%). In 61.7% of individuals with *MECP2*, problematic sleeping was reported (NOS).

Again, by including also male data some differences were noted (**eFigure 4**). No subscale was significant. Furthermore, night laughing, napping and sleepy during the day are no longer significant in the mixed gender groups. Alternatively, difficulty falling asleep (60.3%) and difficulty waking (31.3%) were significant.

Per age-groups in only female *MECP2* samples (**eFigure 5**), only for the 18+ age-group the DA (21.9%, high heterogeneity) and DES (same samples as RTT females) subscales showed significant results. Sleep walking, when applicable, and night waking are significantly prevalent in all age-groups. Night laughing is present in all except the 18+, whereas night screaming is prevalent in the 13–18+ group. Night terror and sleep talking are significant in 8–18+. Teeth grinding is significant in only the 0–7 years old, and nightly unrest in the 18+.

Including the mixed gender samples (**eFigure 6**) but categorizing by age showed that in 0–12 years old DIMS (76.2%, low and 74.4%, high heterogeneity) and in the 18+ years old DA (22.2%, high heterogeneity) were significant. The PR’s of DES and SWTD findings are alike in females

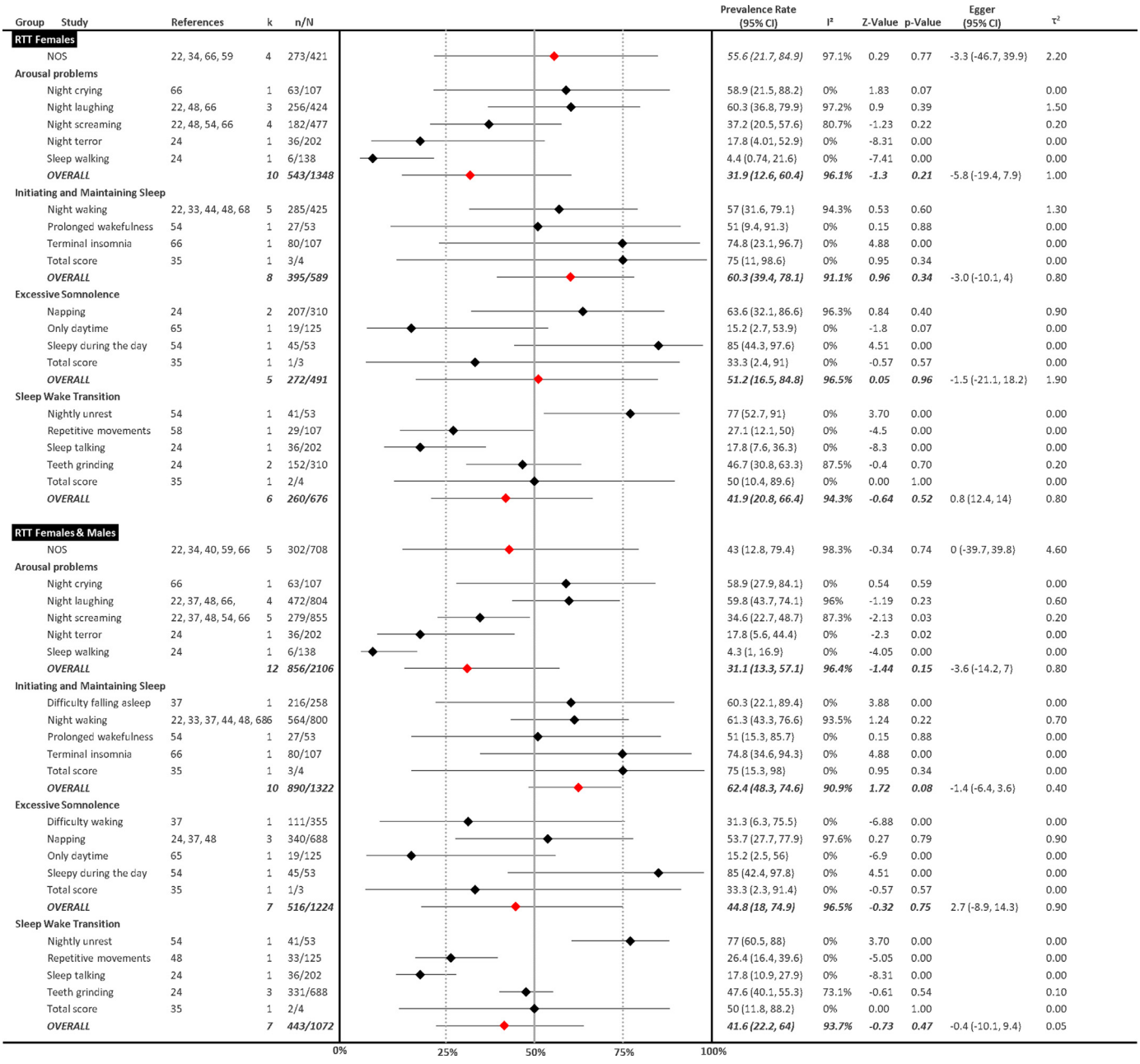

Fig. 2. Forest plot of RTT samples Egger: Egger regression coefficient; I^2: I-squared; k: number of studies, n/N: sample size; prevalence rate: effect size in percentage (%); τ^2: Tau-squared. Grey square is relative weight of the study.

only. Sleep walking was again significant, and so was night waking in all. Night terror and talking was in 8–18+ whereas night screaming in 13–18+ significant. Significant in only one age-group are teeth grinding (0–7 years old), night laughing (0–13 years old) and nightly unrest (18+ years old). Difficulty falling asleep is present in the 0–7 and the 18+ years old.

CDKL5 samples

Females with the diagnosis of *CDKL5* (**eFigure 4**) showed DIMS (59.9%, no heterogeneity), SWTD (33.4%, moderate heterogeneity) being primarily teeth grinding (38%) and repetitive movements (27.1%) and DA (24.3%, no heterogeneity) being mostly night laughing (25.7%) and screaming (22.9%). Insufficient data was available to categorize by age, hence results reflect a broad age-range.

When further including male data (**eFigure 4**) the finding on DIMS became non-significant, but SWTD and DA remained significantly prevalent, also in terms of sleep complaints.

NOS ranged from 58.9 to 59.2% across the gender samples of *CDKL5*. Only one study investigated SDB in females.

FOXG1 samples

No consistent result (**eFigure 4**) was found amongst the datasets reporting on this gene in only female samples.

Clinical profile samples

Only the clinical classification per *MECP2* in females showed a homogenous result; i.e. 31.2% (**eFigure 7**). However, other clinical groups are not significantly different in PR's.

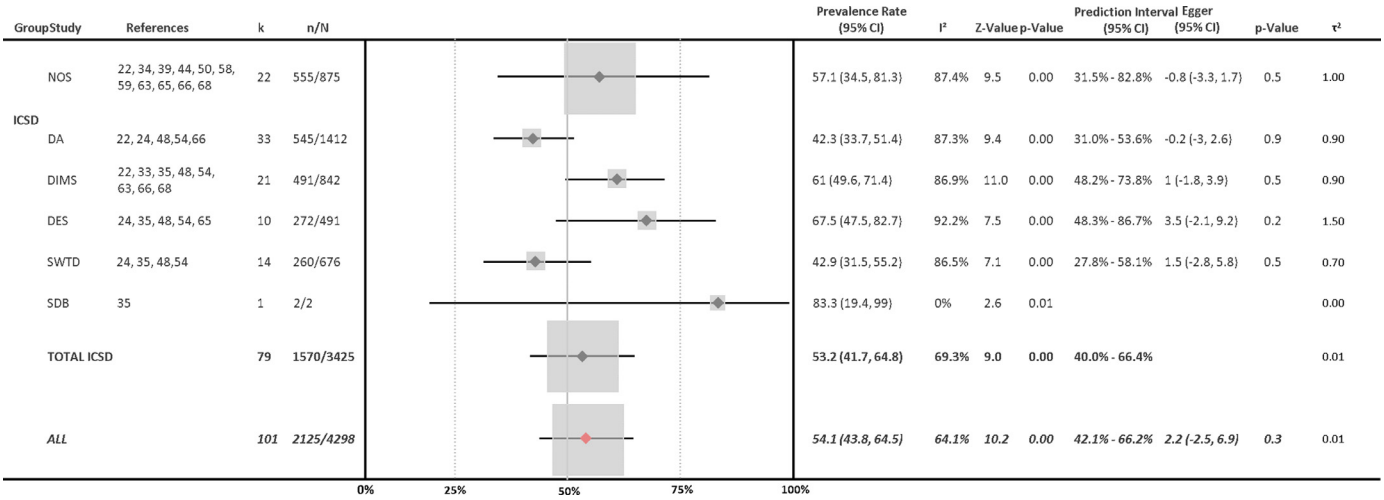

Fig. 3. Forest plot of sleep problems per ICSD subscale Egger: Egger regression coefficient; I^2: I-squared; k: number of studies, n/N: sample size; prevalence rate: effect size in percentage (%); τ^2: Tau-squared.

Aggregated result per the ICSD

The aggregated combination of all relevant studies per the ICSD classification (**Fig. 3**) showed that 54.1% of individuals with RTT exhibit sleep problems. The most prevalent disorders were DES and DIMS, and based on only two subjects SDB. Less than half of the individuals with RTT may also suffer SWTD and DA. Prediction intervals ranges from 27.8% to 86.7%. Disturbed sleep not otherwise specified was reported in 57.1% (95%CI: 34.5% to 81.3%).

Difference tests across the genotypes in female samples (**eFigure 4**), showed that individuals with *MECP2* have significantly more DES ($p<0.00001$) and SWTD problems ($p = 0.002$) than those diagnosed with *CDKL5*.

Compared to prevalence rates reported in the literature in typically developing children

In Spruyt et al. [28,36] the prevalence of DIMS was 30.54% hence in RTT it is two times more prevalent. DA (18.33%) and SWTD (18.46%) are 2.3 times more prevalent, and DES (36.88%) is 1.8 times more prevalent in RTT. Difference test showed that each was significantly higher than typically developing children ($p<0.00001$).

Discussion

Based on 19 studies of RTT sleep complaints, a generic prevalence rate of 54.1% was found. This suggests that more than half of the individuals diagnosed with RTT show problematic sleeping, which persisted throughout their lifespan. In particular, complaints related to disorders of excessive somnolence, and of initiating and maintaining sleep are found as most prevalent. Separately, being sleepy during the day, their nightly unrest as well as sleep behaviors showing difficulties in onset and continuing sleep were most prevalent in RTT. When subcategorized by RTT characteristics, particularly in those with *MECP2* diagnosis primarily night laughing and waking are highly prevalent before the age of 18 years. Older individuals exhibit mostly daytime somnolence. Lastly, in individuals with *MECP2* genotype compared to those affected by *CDKL5*, disorders of excessive somnolence and of sleep wake transition were more prevalent. Few studies reported sleep problems in *FOXG1*. We could conclude that sleep problems were indeed prevalent but also persistent. Findings overall suggest disorders regarding maintenance of the sleep and/or wake state.

The general prevalence of problematic sleeping in our meta-review is lower than previously reported by individual RTT studies [22,24,37]. Yet the highest PR found in our review was for sleepy during the day, which has a prevalence comparable to what is generally reported in the literature. Potential discrepancy in PR's, as supported by our high heterogeneity and non-significant pooled results, might be ascribed to the differences in study design and methodology. For instance, at times it could be the recall bias in family questionnaires during retrospective data collection or the generic sleep screening approach applied. Likewise, and as supported by the quality assessment, studies could improve their reporting of RTT sample characteristics allowing the generation of more precise prevalence rates of aggregated data regarding genetic or other clinical characteristics of RTT. Lastly, given a rare disorder sampling bias from cases collected by potentially overlapping databases, in terms of timeframe or through convenience sampling, might further blur results. The need for a clear sleep research objective is even more demonstrated by the "problematic sleeping" item or "NOS" prevalence rates. That is, our PR remains within the same high range across analyses, whereas the PR's reported in the literature display a very large spread, that is from 10% to 90% [32,34,38-40].

The majority of studies reviewed focused on sleep behaviors assessing DA and SWTD. DA are mental and motor behaviors arising from non-rapid eye movement (NREM) sleep, and commonly associated to stage 1 and stage 2 NREM sleep (or their stage shifts). Whilst the "arousal" is often a partial arousal usually from "deep" sleep also called "slow wave sleep (SWS)" of NREM. Yet shifting between sleep stages, or from wakefulness to sleep may equally provoke parasomnias defined as SWTD. Such state shifts may commonly lead to a confusional state or a "confusional arousal". During such an episode, individuals may present features suggestive of being simultaneously awake and asleep. Although a potential bias as a result of over-investigation of these sleep behaviors may exist, our findings demonstrate that various behaviors may occur during sleep stage shifts ranging from simple to complex activities. A peculiar case is sleep laughing.

Alternatively, another characteristic feature of RTT, namely the presentation of nocturnal seizure with abnormal behavior during sleep might be considered as well. Yet epilepsy is rarely queried and/or reported in those studies reporting on sleep problems in spite of night waking complaints in over 80% of RTT individuals [37]. Difficulties in maintaining sleep of appropriate duration, or frequent short sleep bouts, was furthermore the main finding in the studies that applied animal models [41]. Next, excessive SWS (stage 3 of NREM) fragmentation appears to represent a typical polysomnographic pattern of DA, and therefore suggestive that the restorative aspect of sleep will be severely disrupted. By the same token, SDB is often co-occurring with or triggering other sleep disorders. Respiratory disturbances in RTT are commonly described (i.e., 13/17 patients had the apnea hypopnea index >1.5 events/hour [42]) [43], yet only one study queried this sleep be-

havior; that is in a sample of females with *CDKL5* genotype [35]. These sleep behaviors altogether suggest sleep maintenance problems, or the lack of maturity of the sleep-wake cycle.

Compared to typically developing children, individuals with RTT demonstrated a higher prevalence rate. Age, or even the feature of RTT stage, has been inconsistently reported hampering precise meta-analytic approaches. Although, previous studies [40] [44] [22,37,45] suggest higher prevalence rates in younger and older RTT subjects, we could not fully confirm this. But given that over half of the RTT individuals likely surviving into middle age [44], the persistence of higher than normal rates should not be ignored. That is, caregivers may adjust to the circumstances of nightly poor sleep of the family, yet an outspoken call for therapeutic management of sleep disorders is voiced [46]. Regarding gender, and in the realm of a neurodevelopmental disorder affecting principally girls, such that boys with *MECP2* mutations usually die prenatally [47], our meta-review could not pursue analysis in boys separately. Moreover, too often data reported mixed gender sample percentages, hence our current approach shows but a handful datasets differing between gender samples. Our approach is far from ideal but obviously advocates for more detailed reporting of RTT genetic and clinical characteristics. Next, albeit those three genes share common pathogenic processes thus causing similar phenotypes, *CDKL5* and *FOXG1* only play a partial role in the pathway mediating *MECP2* functions. Our findings suggest that the *MECP2* genotype has higher PR's, especially concerning DES and SWTD. Also the clinical diagnostic features remained often vaguely reported. This despite the fact of being a neurodevelopmental disorder that is commonly diagnosed based on fulfilling clinical criteria [6] and the stipulation of guidelines towards RTT scientific reporting. This lack may likely ensue our non-significant difference between typical and atypical cases. More clear-cut reporting would allow hypothesis driven basic research from a sleep perspective appropriately addressing the neural maturation and synaptogenesis aspect of *MECP2* [13,48]. In light of the recent dispute on the RTT variant related to *CDKL5* (i.e., early seizure onset) to be separately diagnosed as *CDKL5* Deficiency Disorder (CDD) [38,49,50], our findings and analytic approach underline the need for more transparency and completeness in reporting sleep behaviors in RTT, and potentially rare disorders in general.

Several biases towards accurate "numbering" need to be addressed. The studies included noticeably have a selection bias. That is, only seven studies [22,24,35,37,39,40,51] had an unambiguous sleep aim. As a possible result, the poor quality mainly represented issues with "soundness of information" and "analysis, comparability and outcomes". Unfortunately, this applied to the sleep assessment, but equally to the RTT features. The information along the Kerr guidelines [52] was truly insufficient, in particular regarding the classification of the clinical stage, variant types, and age at onset (i.e., early developmental progress) given that some applied retrospective data collection. Information per the Kerr guidelines [52] is essential for comparison purposes. As an example, studies [37,39] and parents experience [53] emphasize that epilepsy was more associated with poor sleep and that medication might impact sleep behaviors [33,54]. We extracted some information alike but could not pursue phenotyping due to scattered data. Subsequently, also a confirmation bias might be present. That is, the incomplete or inconsistent reporting of genes, clinical characteristics or associated features, has certainly complicated the clinical picture displayed in this meta-review. The process of sampling over time, or the unsystematic collection and sharing of sleep data potentially further introduced a sampling bias as well. A potential measurement bias, might be exemplified by the mixed reporting of samples with (un)confirmed genotypes. Similarly, specific sleep questionnaires in the included studies here were rarely used or only applied in the small sample size studies [34,35,51]; for example, such as the Sleep Disturbance Scale for Children (SDSC) (i.e., frequency of problems) and Sleeping Questionnaire for Children with Neurological and other Complex Diseases (SNAKE) (i.e., severity of problems), or a binary generic item have been used. In addition questions might not be tailored to the disease, leading to erroneous PR's. For instance, RTT is characterized by high prevalence of physical disability such that more than half cannot walk independently [37,47] or suffer scoliosis/kyphosis [44–55]. Nonetheless, sleep walking was reported, similarly for "sleep talking" acknowledging that most girls with RTT lose spoken abilities in their onset stage, and such disabilities are more outspoken in atypical cases [47,49]. The CDKL5 genotype dispute, lastly, portrays a chronology bias in data. In general, biases could be avoided when studies and epidemiological reports would implement consensus criteria for reporting sleep behaviors and clinical features in realm of the neurodevelopmental disorder, particularly given that the burden of poor sleep is omnipresent.

A strength of our review is the reporting per the ICSD, and the attempt to homogenize samples to the maximum possible, as well as being the first in RTT. Findings may foster basic research approaches from a sleep perspective, enhancing our understanding of clinical features reported in RTT. This meta-review has also some limitations to address. Few studies had sleep assessment as a primary objective. Regardless of study aims, most of our limitations are related to the lack of consensus in reporting RTT data, e.g., genotypes, clinical characteristics and associated features. As a result, based on the current available data, our PR's remain pooled effect sizes on crude groupings. We moreover cannot ignore the localness of the studies, and potential overlap of datasets, approaches or samples; hence multisite well-designed studies are needed.

We conclude that in individuals with RTT poor sleep is prevalent. That is, they appear to have a disrupted maintenance of sleep (or wakefulness) state. As a result, a wide variety of simple to complex sleep behaviors might be displayed. These may interrupt the nightly rest of the family or relevant others.

Supplementary material

eTable1: Search items in PubMed up to August 2nd 2021
eFigure 1: NIH Quality assessment
eFigure 2: Forest plot of RTT female samples per age-groups
eFigure 3: Forest plot of RTT female and male samples per age-groups
eFigure 4: Forest plot of *MECP2, CDKL5* and *FOXG1* samples
eFigure 5: Forest plot of *MECP2* female samples per age-groups
eFigure 6: Forest plot of *MECP2* female and male samples per age-groups
eFigure 7: Forest plot of clinical profile samples
Supp material.docx

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Findings

A PRISMA guided meta-analysis was conducted on 19 studies. More than half of the individuals with RTT exhibit sleep problems. The three most commonly reported sleep problems were being sleepy during the day, nightly unrest, and trouble initiating and maintaining sleep. Prevalence rates remain roughly unaltered across the lifespan, and sleep problems are about two times more prevalent than in the general population.

Keypoints

Question: What is the prevalence rate of sleep problems in Rett syndrome?

Contributors

Dr. Karen SPRUYT conceived and planned this meta-analytic review. Xinyan ZHANG (XYZ) assisted in the preliminary process.

Meaning

Our findings indicate predominantly disorders in the maintenance of sleep and wake state, and may promote investigations of altered sleep-wake pathogenic mechanisms.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.sleepe.2022.100027.

References

[1] Rett A. Uber ein eigenartiges hirnatrophisches Syndrom bei Hyperammonämie im Kindersalter. *Wien Med Wochenschr* 1966;**116**(37):723–6.
[2] Ellaway C, Christodoulou J. Rett syndrome: clinical characteristics and recent genetic advances. *Disabil Rehabil* 2001;**23**(3–4):98–106.
[3] Laurvick CL, de Klerk N, Bower C, et al. Rett syndrome in Australia: a review of the epidemiology. *J Pediatr* 2006;**148**(3):347–52.
[4] Bienvenu T, Philippe C, De Roux N, et al. The incidence of Rett syndrome in France. *Pediatr Neurol* 2006;**34**(5):372–5.
[5] Kyle SM, Vashi N, Justice MJ. Rett syndrome: a neurological disorder with metabolic components. *Open Biol* 2018;**8**(2).
[6] Neul JL, Kaufmann WE, Glaze DG, et al. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol* 2010;**68**(6):944–50.
[7] Percy AK, Zoghbi HY, Glaze DG. Rett syndrome: discrimination of typical and variant forms. *Brain Dev* 1987;**9**(5):458–61.
[8] Hagberg BA, Skjeldal OH. Rett variants: a suggested model for inclusion criteria. *Pediatr Neurol* 1994;**11**(1):5–11.
[9] 9 Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat Genet* 1999;**23**(2):185–8.
[10] Neul JL, Fang P, Barrish J, et al. Specific mutations in methyl-CpG-binding protein 2 confer different severity in Rett syndrome. *Neurology* 2008;**70**(16):1313–21.
[11] White R, Ho G, Schmidt S, et al. Cyclin-dependent kinase-like 5 (CDKL5) mutation screening in Rett syndrome and related disorders. *Twin Res Hum Genet* 2010;**13**(2):168–78.
[12] Pantaleon FG, Juvier RT. [Molecular basis of Rett syndrome: a current look]. *Rev Chil Pediatr* 2015;**86**(3):142–51.
[13] Mari F, Azimonti S, Bertani I, et al. CDKL5 belongs to the same molecular pathway of MeCP2 and it is responsible for the early-onset seizure variant of Rett syndrome. *Hum Mol Genet* 2005;**14**(14):1935–46.
[14] Roche-Martinez A, Gerotina E, Armstrong-Moron J, Sans-Capdevila O, Pineda M. FOXG1, a new gene responsible for the congenital form of Rett syndrome. *Rev Neurol* 2011;**52**(10):597–602.
[15] Cobolli Gigli C, Scaramuzza L, De Simone M, et al. Lack of Methyl-CpG Binding Protein 2 (MeCP2) Affects Cell Fate Refinement During Embryonic Cortical Development. *Cerebral Cortex (New York, NY* 2018;**28**(5):1846–56 1991.
[16] Spruyt K. A review of developmental consequences of poor sleep in childhood. *Sleep Med* 2019;**60**:3–12.
[17] Tononi G, Cirelli C. Sleep and synaptic homeostasis: a hypothesis. *Brain Res Bull* 2003;**62**(2):143–50.
[18] Glaze DG, Frost JD Jr, Zoghbi HY, Percy AK. Rett's syndrome: characterization of respiratory patterns and sleep. *Ann Neurol* 1987;**21**(4):377–82.
[19] Nomura Y. Early behavior characteristics and sleep disturbance in Rett syndrome. *Brain Dev* 2005;**27**:S35–42 Suppl 1.
[20] Young D, Nagarajan L, de Klerk N, Jacob P, Ellaway C, Leonard H. Sleep problems in Rett syndrome. *Brain Dev* 2007;**29**(10):609–16.
[21] Downs J, Leonard H, Boban S, et al. Sleep problems are pervasive in Rett syndrome and the CDKL5 disorder. *J Intellectual Disabil Res* 2016;**60**(7–8) 779-779.
[22] Wong K, Leonard H, Jacoby P, Ellaway C, Downs J. The trajectories of sleep disturbances in Rett syndrome. *J Sleep Res* 2015;**24**(2):223–33.
[23] Boban S, Leonard H, Wong K, Wilson A, Downs J. Sleep disturbances in Rett syndrome: impact and management including use of sleep hygiene practices. *Am J Med Genetics Part A* 2018;**176**(7):1569–77.
[24] Young D, Nagarajan L, de Klerk N, Jacoby P, Ellaway C, Leonard H. Sleep problems in Rett syndrome. *Brain Dev* 2007;**29**(10):609–16.
[25] Mori Y, Downs J, Wong K, Leonard H. Longitudinal effects of caregiving on parental well-being: the example of Rett syndrome, a severe neurological disorder. *Eur Child Adolesc Psychiatry* 2018;**28**(4):505–20.
[26] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;**6**(7):e1000097.
[27] Zhang X, Lin JS, Spruyt K. Sleep problems in Rett syndrome animal models: a systematic review. *J Neurosci Res* 2021;**99**(2):529–44.
[28] Spruyt K., Cluydts R., Verleye G.B.J.S. Pediatric sleep disorders: exploratory modulation of their relationships. 2004;27(3):495–501.
[29] Diagnostic AAoSMJ, manual c. International classification of sleep disorders. 2005:51–55.
[30] National Heart Lung and Blood Institute. Development and use of quality assessment tools. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools, (Accessed on November 4, 2019).
[31] DelRosso LM, Picchietti DL, Spruyt K, et al. Restless sleep in children: a systematic review. *Sleep Med Rev* 2020;**56**:101406.
[32] Frullanti E, Papa FT, Grillo E, et al. Analysis of the Phenotypes in the Rett Networked Database. *Int J Genomics* 2019;**2019**:6956934.
[33] Zappella M, Genazzani A, Facchinetti F, Hayek G. Bromocriptine in the Rett syndrome. *Brain Dev* 1990;**12**(2):221–5.
[34] Hagebeuk EE, Bijlmer RP, Koelman JH. Poll-The BT. Respiratory disturbances in rett syndrome: don't forget to evaluate upper airway obstruction. *J Child Neurol* 2012;**27**(7):888–92.
[35] Hagebeuk EE, van den Bossche RA, de Weerd AW. Respiratory and sleep disorders in female children with atypical Rett syndrome caused by mutations in the CDKL5 gene. *Dev Med Child Neurol* 2012;**55**(5):480–4.
[36] Spruyt K, O'Brien LM, Cluydts R, Verleye GB, Ferri R. Odds, prevalence and predictors of sleep problems in school-age normal children. *J Sleep Res* 2005;**14**(2):163–176.
[37] Boban S, Wong K, Epstein A, et al. Determinants of sleep disturbances in Rett syndrome: novel findings in relation to genotype. *Am J Med Genetics Part A* 2016;**170**(9):2292–300.
[38] Fehr S, Wilson M, Downs J, et al. The CDKL5 disorder is an independent clinical entity associated with early-onset encephalopathy. *Eur J Hum Genetics: EJHG* 2013;**21**(3):266–73.
[39] Ammanuel S, Chan WC, Adler DA, et al. Heightened delta power during slow-wave-sleep in patients with rett syndrome associated with poor sleep efficiency. *PLoS One* 2015;**10**(10):e0138113.
[40] Leven Y, Wiegand F, Wilken B. Sleep Quality in Children and Adults with Rett Syndrome. *Neuropediatrics* 2020;**51**(3):198–205.
[41] Zhang X, Lin JS, Spruyt K. Sleep problems in Rett syndrome animal models: a systematic review. *J Neurosci Res* 2020.
[42] Amaddeo A, De Sanctis L, Arroyo JO, Khirani S, Bahi-Buisson N, Fauroux B. Polysomnographic findings in Rett syndrome. *Eur J Paediatric Neurol: EJPN: Off J Eur Paediatr Neurol Soc* 2019;**23**(1):214–21.
[43] Zhang X-Y, Spruyt K. Literature cases summarized based on their polysomnographic findings in rett syndrome. *Int J Environ Res Public Health* 2022;**19**(6):3422.
[44] Anderson A, Wong K, Jacoby P, Downs J, Leonard H. Twenty years of surveillance in Rett syndrome: what does this tell us? *Orphanet J Rare Dis* 2014;**9**:87.
[45] Peron A, Canevini MP, Ghelma F, Arancio R, Savini MN, Vignoli A. Phenotypes in adult patients with Rett syndrome: results of a 13-year experience and insights into healthcare transition. *J Med Genet* 2020.
[46] McDougall A., Kerr A.M., Espie CAJJoARiID. Sleep disturbance in children with Rett syndrome: a qualitative investigation of the parental experience. 2005;18(3):201–15.
[47] Leonard H, Cobb S, Downs J. Clinical and biological progress over 50 years in Rett syndrome. *Nature Rev Neurol* 2017;**13**(1):37–51.
[48] Ariani F, Hayek G, Rondinella D, et al. FOXG1 is responsible for the congenital variant of Rett syndrome. *Am J Hum Genet* 2008;**83**(1):89–93.
[49] Mangatt M, Wong K, Anderson B, et al. Prevalence and onset of comorbidities in the CDKL5 disorder differ from Rett syndrome. *Orphanet J Rare Dis* 2016;**11**:39.
[50] Kadam SD, Sullivan BJ, Goyal A, Blue ME, Smith-Hicks C. Rett Syndrome and CDKL5 Deficiency Disorder: from Bench to Clinic. *Int J Mol Sci* 2019;**20**(20).
[51] Merbler AM, Byiers BJ, Garcia JJ, Feyma TJ, Symons FJ. The feasibility of using actigraphy to characterize sleep in Rett syndrome. *J Neurodev Disord* 2018;**10**(1):8.
[52] Kerr AM, Nomura Y, Armstrong D, et al. Guidelines for reporting clinical features in cases with MECP2 mutations. *Brain Dev* 2001;**23**(4):208–11.
[53] McDougall A., Kerr A.M., Espie C.A. Sleep Disturbance in Children with Rett Syndrome: A Qualitative Investigation of the Parental Experience. 2005;18(3):201–15.
[54] McArthur AJ, Budden SS. Sleep dysfunction in Rett syndrome: a trial of exogenous melatonin treatment. *Dev Med Child Neurol* 1998;**40**(3):186–92.

[55] Halbach NS, Smeets EE, Schrander-Stumpel CT, van Schrojenstein Lantman de Valk HH, Maaskant MA, Curfs LM. Aging in people with specific genetic syndromes: rett syndrome. *Am J Med Genetics Part A* 2008;**146a**(15):1925–32.
[56] Guerrini R, Parrini E. Epilepsy in Rett syndrome, and CDKL5- and FOXG1-gene-related encephalopathies. *Epilepsia* 2012;**53**(12):2067–78.
[57] Trevathan E, Moser HW. TRSDCWG. Diagnostic criteria for Rett syndrome. *Ann Neurol* 1988;**23**(4):425–8.
[58] Mori Y, Downs J, Wong K, Heyworth J, Leonard H. Comparing parental well-being and its determinants across three different genetic disorders causing intellectual disability. *J Autism Dev Disord* 2017;**48**(5):1651–65.
[59] Pini G, Bigoni S, Congiu L, et al. Rett syndrome: a wide clinical and autonomic picture. *Orphanet J Rare Dis* 2016;**11**(1):132.
[60] Cianfaglione R, Clarke A, Kerr M, Hastings RP, Oliver C, Felce D. A National Survey of Rett Syndrome: age, Clinical Characteristics, Current Abilities, and Health. *Am J Med Genetics Part A* 2015;**167**(7):1493–500.
[61] Hagberg B. Clinical manifestations and stages of Rett syndrome. *Ment Retard Dev Disabil Res Rev* 2002;**8**(2):61–5.
[62] listed Na. Diagnostic criteria for Rett syndrome. The Rett Syndrome Diagnostic Criteria Work Group. *Ann Neurol* 1988;**23**(4):425–8.
[63] Hagberg B, Hanefeld F, Percy A, Skjeldal O. An update on clinically applicable diagnostic criteria in Rett syndrome. Comments to Rett Syndrome Clinical Criteria Consensus Panel Satellite to European Paediatric Neurology Society Meeting, Baden Baden, Germany. *Eur J Paediatric Neurol: EJPN: Off J Eur Paediatr Neurol Soc* 2001;**6**(5):293–7 2002.
[64] Vignoli A, La Briola F, Peron A, et al. Medical care of adolescents and women with Rett syndrome: an Italian study. *Am J Med Genetics Part A* 2012;**158a**(1):13–18.
[65] Leonard H, Bower C. Is the girl with Rett syndrome normal at birth? *Dev Med Child Neurol* 1998;**40**(2):115–21.
[66] Cooper RA, Kerr AM, Amos PM. Rett syndrome: critical examination of clinical features, serial EEG and video-monitoring in understanding and management. *Eur J Paediatric Neurol: EJPN: Off J Eur Paediatr Neurol Soc* 1998;**2**(3):127–35.
[67] Sansom D, Krishnan VH, Corbett J, Kerr A. Emotional and behavioural aspects of Rett syndrome. *Dev Med Child Neurol* 1993;**35**(4):340–5.
[68] Hagberg B, Goutières F, Hanefeld F, Rett A, Wilson J. Rett syndrome: criteria for inclusion and exclusion. *Brain Dev* 1985;**7**(3):372–3.
[69] Coleman M, Brubaker J, Hunter K, Smith G. Rett syndrome: a survey of North American patients. *J Ment Defic Res* 1988;**32**(2):117–24 Pt.