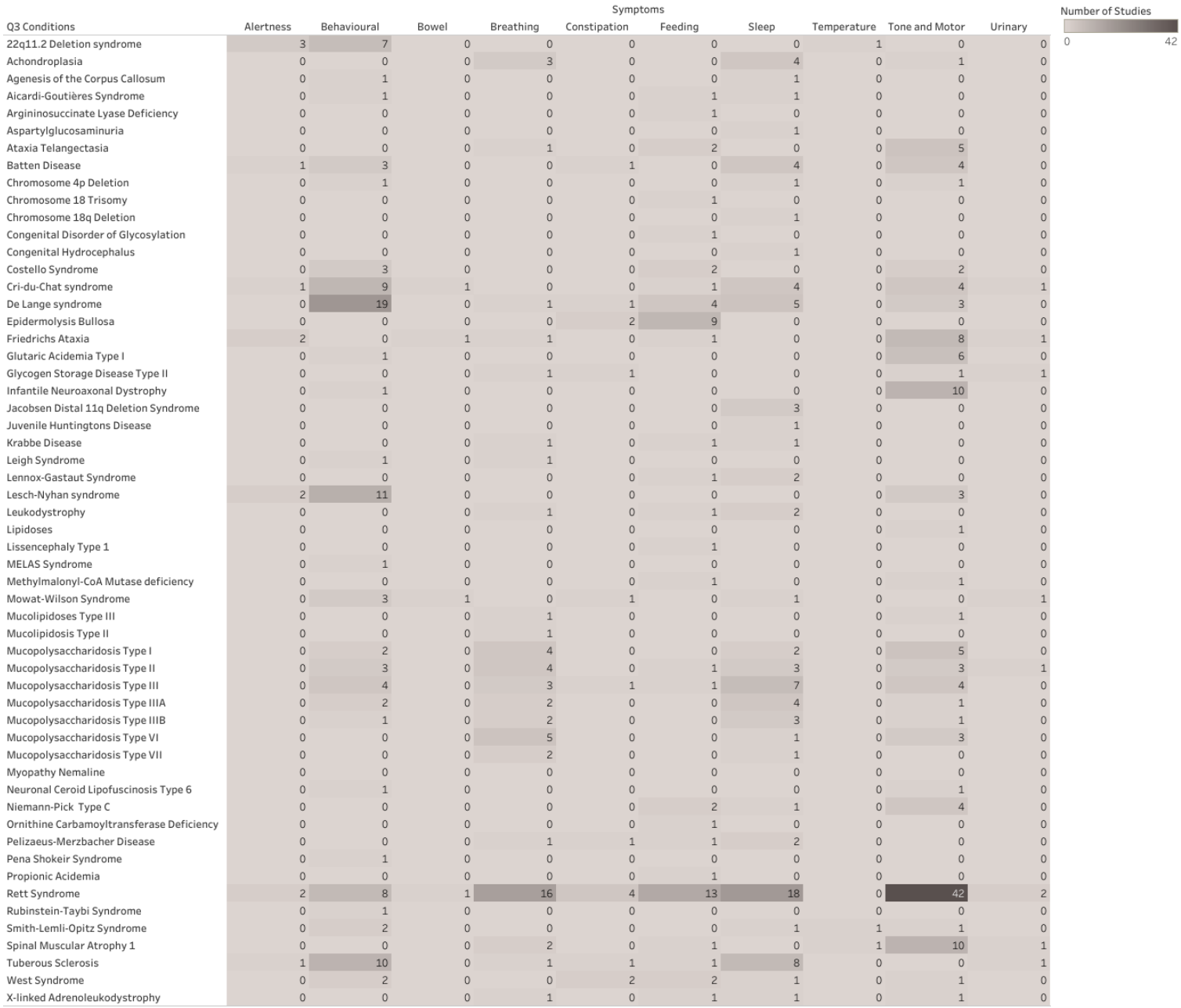
Supplementary File 2

Figure 1: Heat map of Q3 conditions and symptoms



Q3 Conditions	Symptoms									
	Alertness	Behavioural	Bowel	Breathing	Constipation	Feeding	Sleep	Temperature	Tone and Motor	Urinary
22q11.2 Deletion syndrome	3	7	0	0	0	0	0	1	0	0
Achondroplasia	0	0	0	3	0	0	4	0	1	0
Agenesis of the Corpus Callosum	0	1	0	0	0	0	1	0	0	0
Aicardi-Goutières Syndrome	0	1	0	0	0	1	1	0	0	0
Argininosuccinate Lyase Deficiency	0	0	0	0	0	1	0	0	0	0
Aspartylglucosaminuria	0	0	0	0	0	0	1	0	0	0
Ataxia Telangectasia	0	0	0	1	0	2	0	0	5	0
Batten Disease	1	3	0	0	1	0	4	0	4	0
Chromosome 4p Deletion	0	1	0	0	0	0	1	0	1	0
Chromosome 18 Trisomy	0	0	0	0	0	1	0	0	0	0
Chromosome 18q Deletion	0	0	0	0	0	0	1	0	0	0
Congenital Disorder of Glycosylation	0	0	0	0	0	1	0	0	0	0
Congenital Hydrocephalus	0	0	0	0	0	0	1	0	0	0
Costello Syndrome	0	3	0	0	0	2	0	0	2	0
Cri-du-Chat syndrome	1	9	1	0	0	1	4	0	4	1
De Lange syndrome	0	19	0	1	1	4	5	0	3	0
Epidermolysis Bullosa	0	0	0	0	2	9	0	0	0	0
Friedrichs Ataxia	2	0	1	1	0	1	0	0	8	1
Glutaric Acidemia Type I	0	1	0	0	0	0	0	0	6	0
Glycogen Storage Disease Type II	0	0	0	1	1	0	0	0	1	1
Infantile Neuroaxonal Dystrophy	0	1	0	0	0	0	0	0	10	0
Jacobsen Distal 11q Deletion Syndrome	0	0	0	0	0	0	3	0	0	0
Juvenile Huntingtons Disease	0	0	0	0	0	0	1	0	0	0
Krabbe Disease	0	0	0	1	0	1	1	0	0	0
Leigh Syndrome	0	1	0	1	0	0	0	0	0	0
Lennox-Gastaut Syndrome	0	0	0	0	0	1	2	0	0	0
Lesch-Nyhan syndrome	2	11	0	0	0	0	0	0	3	0
Leukodystrophy	0	0	0	1	0	1	2	0	0	0
Lipidoses	0	0	0	0	0	0	0	0	1	0
Lissencephaly Type 1	0	0	0	0	0	1	0	0	0	0
MELAS Syndrome	0	1	0	0	0	0	0	0	0	0
Methylmalonyl-CoA Mutase deficiency	0	0	0	0	0	1	0	0	1	0
Mowat-Wilson Syndrome	0	3	1	0	1	0	1	0	0	1
Mucolipidoses Type III	0	0	0	1	0	0	0	0	1	0
Mucolipidosis Type II	0	0	0	1	0	0	0	0	0	0
Mucopolysaccharidosis Type I	0	2	0	4	0	0	2	0	5	0
Mucopolysaccharidosis Type II	0	3	0	4	0	1	3	0	3	1
Mucopolysaccharidosis Type III	0	4	0	3	1	1	7	0	4	0
Mucopolysaccharidosis Type IIIA	0	2	0	2	0	0	4	0	1	0
Mucopolysaccharidosis Type IIIB	0	1	0	2	0	0	3	0	1	0
Mucopolysaccharidosis Type VI	0	0	0	5	0	0	1	0	3	0
Mucopolysaccharidosis Type VII	0	0	0	2	0	0	1	0	0	0
Myopathy Nemaline	0	0	0	0	0	0	0	0	0	0
Neuronal Ceroid Lipofuscinosis Type 6	0	1	0	0	0	0	0	0	1	0
Niemann-Pick Type C	0	0	0	0	0	2	1	0	4	0
Ornithine Carbamoyltransferase Deficiency	0	0	0	0	0	1	0	0	0	0
Pelizaeus-Merzbacher Disease	0	0	0	1	1	1	2	0	0	0
Pena Shokeir Syndrome	0	1	0	0	0	0	0	0	0	0
Propionic Acidemia	0	0	0	0	0	1	0	0	0	0
Rett Syndrome	2	8	1	16	4	13	18	0	42	2
Rubinstein-Taybi Syndrome	0	1	0	0	0	0	0	0	0	0
Smith-Lemli-Opitz Syndrome	0	2	0	0	0	0	1	1	1	0
Spinal Muscular Atrophy 1	0	0	0	2	0	1	0	1	10	1
Tuberous Sclerosis	1	10	0	1	1	1	8	0	0	1
West Syndrome	0	2	0	0	2	2	1	0	1	0
X-linked Adrenoleukodystrophy	0	0	0	1	0	1	1	0	1	0

Number of Studies
0 42

Table 1: Characteristics of included studies with a single symptom

First Author Year of Publication	Study Design	Q3 Condition(s)	Number of participants	Tools or Scales Used	Study Objective; Intervention(s)	Primary Outcome(s) / Conclusion(s)
Alertness						
Bossie 2017[1]	Cross-sectional	Friedrich's ataxia	16 + 10 controls (3 children)	TEF	Describes trajectory or characteristics	No difference between FA and controls in mitochondrial capacity, but HA has lower muscle endurance and lower feelings of physical energy.
de Vries 2009[2]	Cross-sectional	Tuberous sclerosis	37 + 37 sibling controls	CPRS, TEA-CH	Describes trajectory or characteristics	TSC group had significantly more neuropsychological attention deficits
Fabio 2009[3]	Case Control	Rett syndrome	10 + 10 controls	VABS	Describes trajectory or characteristics	Children with Rett have deficits in ability to pay attention to selective sources of information.
Looman 2010[4]	Cross-sectional	22q11.2 deletion syndrome	45 + 10,343 healthy controls and 683 with chronic conidtions	PedsQL Multidimensional Fatigue Scale, 22qFamily Matters Survey	Describes trajectory or characteristics	Children with 22q11.2 deletion have significantly more fatigue than controls.
Parrish 2012[5]	Cross-sectional	Acquired demyelinating syndromes	49 + 92 healthy controls	PedsQL Multidimensional Fatigue Scale	Describes trajectory or characteristics	Parent and self-report showed elevated fatigue symptoms in comparison to controls.
Paulsen 2010[6]	Tool / Scale Development	Friedrich's ataxia	43 + 43 healthy controls	PedsQL Generic Core and Multidimensional Fatigue Scale	Tool or scale development	Children with FA had higher fatigue scores than controls. More studies are needed to validate the PedQL Fatigue Scales in this population.
Quintero[7] 2014	Cross-sectional	22q11.2 deletion syndrome	32 with VCFS + 55 with other conditions + 42 healthy controls	Attention Network Test, Flanker Test	Describes trajectory or characteristics	The control but not the implementation of attention is selectively impaired in girls with 22q11.2 deletion and but all attentional efficiency improves with age.

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Behavioral Problems						
Adams 2006[8]	Cross-sectional	NCL3, NCL6	26	CBCL, SIB-R, Y-BOCS	Describes trajectory or characteristics	Participants showed a broad range of behavioral and psychiatric problems that can be used as a quantitative baseline to measure further decline.
Anderson 1976[9]	Case Series	Lesch-Nyhan syndrome	4	Number of biting attempts, Behavior assessed on scale of 1-5	Pharmacologic intervention; L-5-hydroxyl-tryptophan	No change in self-mutilation seen
Anderson 1977,[10] 1978[11]	Case Series	Lesch-Nyhan syndrome	5	Finger to mouth contacts per minute	Psychological intervention; Aversive stimulation (electric shock) / Positive reinforcement and / or time-out	Positive reinforcement and/or time-out led to reductions in self-injury, punishment encouraged self-injury
Anderson 1994[12]	Cross-sectional	Lesch-Nyhan syndrome	40	-	Describes trajectory or characteristics	Severity of self-injury does not change over time and earlier the age of onset of self-injury the worse it became.
Arron 2011[13]	Cross-sectional	Cri-du-Chat, De Lange syndrome	741 (58 with CdC, 101 with DL)	RBQ	Describes trajectory or characteristics	High prevalence of self-injury in this population; self-injury associated with repetitive and impulsive behavior.
Aneja 2007[14]	Case control	22q11.2 deletion syndrome	86 + 36 controls with ADHD	CBCL	Describes trajectory or characteristics	Participants with 22q11.2 deletion had elevated scores on the CBCL
Basile 2007[15]	Cross-sectional	De Lange syndrome	56	DBC-P	Describes trajectory or characteristics	Participants showed variable behavioral characteristics consistent with CdLS, including hyperactivity, attention disorder, anxiety, compulsive disorders, self-injurious behavior and autistic-like features.

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Clarke 1998[16]	Cross-sectional, Survey	Cri-du-chat	38 CdC + 75 other conditions	ABC	Describes trajectory or characteristics	CdC associated with greater ratings of problems behaviors on at least one ABC subscale than comparison groups with intellectual disability.
Cornish 1998[17]	Cross-sectional	Cri-du-chat	20	VABS	Describes trajectory or characteristics	50% of participants had externalizing behaviors, including poor concentration, hyperactivity and impulsiveness.
Cross 2014[18]	Cross-sectional	MPS III	20 + 25 with Intellectual Disability	VABS, ABC, EDBI, SBRS	Describes trajectory or characteristics	Middle phase (2-9 years) of MPS III associated with greater frequency of challenging behaviors than late phase (10-15 years)
Duijff 2013[19]	Longitudinal Study	22q11.2 deletion syndrome	53	CNCL	Describes trajectory or characteristics	As children with 22q11.2 deletion get older internalizing behaviors increase while externalizing behaviors decrease.
Dykens 1997[20]	Cross-sectional	Cri-du-chat	146	ABC	Describes trajectory or characteristics	Children with CdC show hyperactivity, aggression, tantrums and self-injurious behavior.
Eden 2014[21]	Cross-sectional	De Lange syndrome, tuberous sclerosis	37 with TS + control of 404, 61 with CdLS	CBQ, Wessex Behaviour Schedule, RBQ,	Describes trajectory or characteristics	Rates of self-injury and aggression were high, but not significantly higher than children in the control groups; both self-injury and aggression were associated with stereotyped and pain behaviors, low mood, hyperactivity, impulsivity and repetitive language use.
Eom 2017[22]	Cross-sectional	Leigh syndrome, mitochondrial disorders, MELAS syndrome	16 with LS, 3 with MELAS, 51 non-specific MD	CBCL	Describes trajectory or characteristics	Mean score of total behavioral problem was close to clinical cutoff score and 43% were within in clinical range.
Fabbro 2012[23]	Cross-sectional	22q11.2 deletion syndrome	74	VABS	Describes trajectory or characteristics	Lower adaptive behavior scores were strongly associated with high depression or anxiety scores, lower IQ and higher age.

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Feinstein 2002[24]	Case control	22q11.2 deletion syndrome	28 + 29 cognitively matched controls	CBCL	Describes trajectory or characteristics	CBCL score were elevated in comparison to general population, but not significantly higher than matched controls.
Freeman 2013[25]	Cross-sectional	Smith-Lemli-Opitz syndrome	13	Behavior Problem Questionnaire	Describes trajectory or characteristics	Greater severity of cholesterol synthesis defect correlated with severity of challenging behaviors.
Galera 2006[26]	Cross-sectional	Costello syndrome	11 + 33 controls	CBCL	Describes trajectory or characteristics	CS had significantly higher Internalizing Problems, but not Externalizing Problems than controls.
Hall 2001[27]	Longitudinal	Lesch-Nyhan syndrome	3	-	Describes trajectory or characteristics	Parents reported that self-injury began suddenly and violently; self-injury may occur more frequently when child is left alone.
Hyman 2002[28]	Cross-sectional	De Lange syndrome	88	Wessex Scale, The Self-Restraint Checklist, Compulsive Behavior Checklist	Describes trajectory or characteristics	Found a significant association between self-injurious behavior and self-restraint, with those displaying both having significantly more compulsive behavior.
Jansen 2007[29]	Case control	22q11.2 deletion syndrome	69 with VCFS + 69 controls	CBCL	Describes trajectory or characteristics	Children with 22q11.2 deletion showed more behavioral problems than control.
Khasnavis 2016[30]	RCT	Lesch-Nyhan syndrome	8 + 1 adult	BPI	Pharmacologic intervention; Ecopipam	Appears to reduce self-injury, but study terminated early due to side effects.
Klaassen 2013[31]	Case control	22q11.2 deletion syndrome	90 + 33 control	CBCL	Describes trajectory or characteristics	About 30% of children with 22q11.2 deletion are above the 97th percentile for at least one behavior subscale on the CBCL.
Kopp 2008[32]	Cross-sectional	Tuberous sclerosis	87	BSI-2	Describes trajectory or characteristics	40% showed of children with TS clinically significant behavioral problems and 50% of their parents reported significant parenting stress.

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Lal 2016[33]	Cross-sectional	De Lange syndrome	15	ABC	Describes trajectory or characteristics	14 of the 15 children had abnormal scores in more than one behavioral area and these behavioral problems can exist in children with normal brain structure.
Leclezio 2015[34]	Tool / Scale Development	Tuberous sclerosis	62 caregivers of children with TS	TAND Checklist	Tool or scale development	Pilot validation suggests that the TAND Checklist is a useful tool for behavioral problems in TS.
Moss 2005[35]	Cross-sectional	De Lange syndrome	8	CBI	Describes trajectory or characteristics	7 of the 8 participants showed self-injurious behavior that was associated with a particular setting events.
Mulder 2017[36]	Systematic Review	De Lange syndrome	-	-	Describes trajectory or characteristics	There is a lack of uniform and validated assessment tools used in studies of this population.
Nelson 2014[37]	Longitudinal, Survey	Cri-du-chat, De Lange syndrome	42 with CdC, 67 with DLS, 142 controls with other conditions	RBQ, MIPQ	Describes trajectory or characteristics	DLS showed significantly lower levels of mood, interest and pleasure than CDC and control group.
Nyhan 1980[38]	Case Series	Lesch-Nyhan syndrome	9	-	Pharmacologic intervention; 5-hydroxy-tryptophan	Immediate reduction in self-injurious behavior, but after 1-3 months this reduction disappeared.
Oliver 2006[39]	N of 1 Trials	De Lange syndrome	16	CBI, Coding system for videotaped behaviors	Describes trajectory or characteristics	For 9 of the participants self-injury was related to levels of adult attention, showing SIB can be affected by environmental factors.
Oliver 2008[40]	Case control	De Lange syndrome	54 with DLS + 46 matched controls	CBI, ISQ, ABC, CBC, Frequency of behavior	Describes trajectory or characteristics	No difference between groups in global behavior disorder.

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Oliver 2009[41]	Case control	De Lange syndrome	54 with CdLS + 46 matched controls	CBI, ISQ, ABC, CBC, Frequency of behavior	Describes trajectory or characteristics	Self-injurious behavior was not more prevalent in DLS then the controls, but was predicted by hyperactivity, stereotyped and compulsive behaviors.
Oliver 2012[42]	Cross-sectional	Children with severe intellectual disability	943	WBS	Describes trajectory or characteristics	High frequency repetitive or ritualistic behavior associated with great risk of self-injury and showing two or more sever challenging behaviors.
Robey 2003[43]	Cross-sectional	Lesch-Nyhan syndrome	64	Questionnaire designed for study	Describes trajectory or characteristics	Most common forms of self-injury was biting of lip and/or fingers.
Rojahn 2001[44]	Tool / Scale Development	Unspecified ID	1122	BPI, ABC, NCBRF, DASH-II	Tool or scale development	BPI is a valid tool; 43% of participants showed self-injury, 54% showed stereotyped behavior, 38% showed aggressive behavior.
Rojahn 2012[45]	Tool / Scale Development	Unspecified ID	1122	BPI, BFI-S	Tool or scale development	BPI Short Form is equally sensitive compared to original BPI.
Rojahn 2013[46]	Cross-sectional, Tool / Scale Development	De Lange syndrome	180	BPI, BFI-S	Describes trajectory or characteristics	BPI and BPI-S are both valid tools for behavioral problems in intellectual disabilities.
Shapiro 2015[47]	Longitudinal, Tool / Scale Development	MPSIII	25	SBRS	Describes trajectory or characteristics	The SBRS is a valid scale in MPSIII
Sloneem 2009[48]	Case Control	De Lange syndrome	47 + 17 matched controls	CBI, Operational definitions of self-injury	Psychological intervention; Environmental conditions: demand, denial, attention, no contact	The association between environment and self-injury in DLS did not differ from the controls.
Srivastava 2014[49]	Cross-sectional	De Lange syndrome	41	CARS, ABC, VABS	Describes trajectory or characteristics	The highest ABC subscales in children with DLS were Hyperactivity and Irritability.

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Staley 2008[50]	Retrospective Chart Review	Tuberous sclerosis	257	-	Describes trajectory or characteristics	10% of children with TS showed SIB.
Teixeira 2011[51]	Cross-sectional	Cri-du-chat	10	The Psychoeducational Profile - Revised	Describes trajectory or characteristics	The number of maladaptive behaviors was difference between the participants.
Uesugi 2010[52]	Cross-sectional	Mowat-Wilson syndrome, Pena Shokeir syndrome, tuberous sclerosis , West syndrome	6 with Q3 conditions, 20 with other conditions	ABC	Describes trajectory or characteristics	Most common behavioral problem subscales were Irritability and Lethargy, both of which were higher than in controls
Uesugi 2013[53]	Cross-sectional	Mowat-Wilson syndrome, Pena Shokeir syndrome, tuberous sclerosis , West syndrome	86	ABC	Describes trajectory or characteristics	No significant differences between levels of intellectual disability and behavioral subscales, expect for stereotypy and lethargy
Yagihashi 2012[54]	Cross-sectional	Rubinstein-Taybi syndrome	63	CBCL	Describes trajectory or characteristics	Older group shoed higher scores in Anxious/Depression and Aggressive Behavior.
Breathing Difficulties						
Afsharpaiman 2011[55]	Retrospective Chart Review	Achondroplasia	46	-	Describes trajectory or characteristics	25 of the 46 participants had obstructive sleep apnea.
Corben 2013[56]	Longitudinal	Friedrich's ataxia	82	ESS	Describes trajectory or characteristics	21% of the participants were diagnosed with obstructive sleep apnea, showing the importance of regular screenings in this population.
Finkel 2014[57]	Longitudinal	SMA1	7	-	Describes trajectory or characteristics	Respiratory muscle strength a deteriorating trend over time.
Hagebeuk 2012[58]	Cross-sectional	Rett syndrome	12	SDSC	Describes trajectory or characteristics	In 8 children central apneas present during the day often with obstructive apneas at night; polysomnography is recommended.

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John 2011[59]	Cross-sectional	MPSVI	28	-	Describes trajectory or characteristics	Snoring, witnessed apnea and macroglossia common findings in this population.
Julu 2001[60]	Case Control	Rett syndrome	4	-	Describes trajectory or characteristics	Respiratory rhythm was normal during sleep and abnormal when awake.
Mackay 2017[61]	Cross-sectional	Rett syndrome	413	Questionnaire designed for study	Describes trajectory or characteristics	Breath-holding reported in 69% of RS participants, hyperventilation in 46% and abdominal bloating in 42%.
Mellies 2004[62]	Case Series, Longitudinal	SMA1	6 with SMA1 + 1 with SMA2	Questionnaire designed for study	Physical intervention; Non-invasive (positive pressure) ventilation	Non-invasive ventilation during sleep completely eliminated disordered breathing.
Mogayzel 1998[63]	Retrospective chart review	Achondroplasia	88	-	Describes trajectory or characteristics	The majority of patients did not have OSA or central apnea, but a substantial minority are severely affected.
Myer 1990[64]	RCT	Leigh syndrome	3 with LS + 11 with other diagnoses	-	Pharmacologic intervention; Oral naltrexone	No apneic events occurred during naltrexone therapy, but reoccurred when treatment was discontinued.
Nabatame 2009[65]	Retrospective Chart Review	Glycogen storage disease type II	4	-	Physical intervention; Non-invasive (positive pressure) ventilation	Sleep-related symptoms resolved, but no improvement in respiratory function over 2 year follow-up period.
Pieper 2018[66]	Systematic Review	Complex chronic conditions	-	-	Pharmacological and physical interventions; various	Evidence for effectiveness of treatment approaches for dyspnea is low.
Rohdin 2007[67]	Case Series	Rett syndrome	12	-	Describes trajectory or characteristics	All subjects showed apnea, shallow breathing or hypoventilation when awake and asleep.

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Kasapkara 2014[68]	Cross-sectional	MPS I, MPS II, MPS VI	19	-	Describes trajectory or characteristics	Study showed severe OSA in 11 participants and moderate in 2; home sleep studies are quick and accessible screening methods.
Schulter 1995[69]	Case-series	Rett syndrome	2	-	Describes trajectory or characteristics	Study showed primary hyperventilation that lead to hypocapnia and apnea. In younger patient this occurred only during awake state, but in older patient this occurred when awake and asleep.
Semenza 1988[70]	Retrospective Chart Review	MLII, MLIII, MPSI, MPSII, MPSVI	21	-	Surgical and pharmacologic interventions; Tonsillectomy, adenoidectomy, tracheostomy, diuretics, theophylline, digoxin, beta adrenergic blockers, calcium antagonists	Respiratory problems in ML and MPS are complex and multifactorial.
Sudarsan 2014[71]	RCT	MPSI, MPSII, MPSIII, MPSIIIA, MPSIIIB, MPSVI, MPSVII	32 with MPS + 48	ESS-C	Surgical and physical interventions; Adenotonsillectomy vs. CPAP	Both groups showed significant improvement, with CPCP showing immediate improvement.
Tenconi 2017[72]	Retrospective Chart Review	Achondroplasia	43	-	Surgical and physical interventions; ENT surgery, CPAP, BiPAP, cervical decompression	OSA is common in children with Achondroplasia.
Vilozni 2010[73]	Longitudinal	Ataxia telangectasia	28	-	Describes trajectory or characteristics	Rapid lung function deterioration occurs with respiratory infection.
Waters 1993[74]	Cross-sectional	Achondroplasia	20 (15 children)	-	Describes trajectory or characteristics	All participants had upper airways obstruction.

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Waters 1995[75]	Case Series	Achondroplasia	21	-	Surgical and physical interventions; Adenotonsillectomy, losing weight, CPAP	Sleep studies after interventions show reduction in respiratory disturbance index.
Weese-Mayer 2006[76]	Case Control	Rett syndrome	47 + 47 matched controls	LifeShirt	Describes trajectory or characteristics	Breathing was more irregular, with increased breathing frequency, mean airflow and hear rate in RS than in the controls.
Weese-Mayer 2008[77]	Case-control	Rett syndrome	47 + 47 controls	LifeShirt	Describes trajectory or characteristics	Breathing was more irregular with increased breathing frequency in daytime compared to nighttime.
Constipation						
Haynes 1997[78]	Open-label	Epidermolysis bullosa	20	Questionnaire developed for study	Pharmacologic intervention; Fiber-containing liquid formula (Enrich)	All participants showed substantial improvement in constipation.
Murata 2017[79]	Retrospective Chart Review	NCL3, Pelizaeus-Merzbacher bisease, tuberous sclerosis, West syndrome	59	Constipation severity measure on numeric scale, Bristol Stool Scale	Pharmacologic intervention; Carnitine	Constipation improved after supplementation with carnitine.
Feeding Difficulties						
Alshammari 2011[80]	Retrospective Chart Review	Epidermolysis bullosa	49 (7 with EB)	Success judged as taking food by mouth, no dysphagia, no vomiting, good weight gain and not residual stricture	Surgical intervention; Endoscopic balloon dilatation	Treatment successful in 86% of patients

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Anderson 2004[81]	Cross-sectional	Epidermolysis bullosa	53	Dysphagia score (0-4)	Surgical intervention; Endoscopic balloon dilatation	50 of 53 had improvement in dysphagia score.
Azizkhan 2006[82]	Retrospective Chart Review	Epidermolysis bullosa	25	-	Surgical intervention; Fluoroscopically guided balloon dilatation	Most patients had immediate relief of symptoms, rapid recovery and able to take food within 1 day
Blommaert 2016[83]	Case Series	MEGDEL syndrome	4	DSFS	Surgical and pharmacologic intervention; Bilateral submandibular gland excision and parotid duct ligation, advice to interrupt tongue protrusion, adenotonsillectomy, feeding advice, antireflux medication	Each patient needs stepwise, personalized treatment
Bruns 2013[84]	Longitudinal	Chromosome 18 trisomy	10	Tracking Rare Incidence Syndromes Feeding Protocol	Describes trajectory or characteristics	Description of primary feeding methods and identification and treatment of gastroesophageal reflux.
Fortunato 2008[85]	Case Series	Rett syndrome	32	-	Describes trajectory or characteristics	Participants with GERD or dysphagia had more swallows followed by abnormal esophageal peristalsis compared to those without symptoms.
Gollu 2017[86]	Retrospective Chart Review	Epidermolysis bullosa	9 (7 children)	Dysphagia score (0-4)	Surgical intervention; Endoscopic balloon dilatation	7 participants can easily swallow solid food, but 2 have some difficulties in swallowing between dilatations.

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Hyman 1987[87]	Case Series	Argininosuccinate kyase deficiency, MCM deficiency, ornithine carbamoyltransferase deficiency disease, propionic acidemia	6	Percent of offered bites, number of inappropriate behaviors	Psychological intervention; Positive reinforcement and guidance techniques	5 children responded to treatment and for them food acceptance increased.
Isaacs 2003[88]	Retrospective Chart Review	Rett syndrome	22 + 22 matched controls	Nutrition assessment	Describes trajectory or characteristics	Significant difference in feeding skills and irregular breathing patterns that may interfere with eating reported significantly more in RS than control group.
Kawahara 2007[89]	Case Series	Profound neurological impairment	8 (6 children)	24 hour esophageal pH study	Pharmacologic; rikkunshito	Rikkunshito reduced the frequency of emesis in 3 patients and mean percentage time of esophageal and mean duration of reflux decreased significantly.
Kawai 2004[90]	Open Label	De Lange syndrome, West syndrome	4 + 4 with Cerebral Palsy	Frequency of emesis (score 1 to 5)	Pharmacologic intervention; Baclofen	Frequency of emesis significantly decreased with baclofen treatment.
Keage 2017[91]	Cross-sectional	Friedrich's ataxia	60	Swal-QOL, FARS	Describes trajectory or characteristics	98% of participants reported dysphagia; no reliable predictors of penetration or aspiration were identified.
Lefton-Greif 2000[92]	Cross-sectional	Ataxia telangectasia	70 (unclear how many chidren	-	Describes trajectory or characteristics	27% of participants with dysphagia demonstrated aspiration; those who aspirated had significantly lower weight.
Lefton-Greif 2016[93]	Cross-sectional	Ataxia telangectasia	20 + 82 matched controls	-	Describes trajectory or characteristics	Safe expiratory patterns of peri-deglutitive airflow occurred significantly less often in AT than in controls.
Luzzani 2003[94]	Case Series	De Lange syndrome	43	-	Describes trajectory or characteristics	Confirms the high incidence of GER in DLS regardless of clinical phenotype.

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Markos 2016[95]	Case Series	Epidermolysis bullosa	6 (2 children)	Mean dysphagia free interval	Surgical intervention; Esophageal stricture dilatation	Dysphagia free interval for 2 children participants was 4 and 9 months.
Mezzedimi 2017[96]	Cross-sectional	Rett syndrome	61	Dysphagia severity (scale 0-3)	Describes trajectory or characteristics	Progressive feeding deterioration reported by caregivers.
Morgan 2008[97]	Cross-sectional	Rett syndrome	9 + 9 matched controls	CAPND, DOSS, pulse oximetry	Describes trajectory or characteristics	Pulse oximetry may be useful for dysphagia screening.
Morton 1997[98]	Cross-sectional	Rett syndrome	20 (18 children)	Videofluoroscopy abnormalities (scale 0-3), Chewing score (scale 0-3), Carer's feeding score (scale 0-3)	Describes trajectory or characteristics	All participants had reduced tongue movements with premature spillover into the pharynx and delayed pharyngeal swallow.
Morton 2000[99]	Cross-sectional	Rett syndrome	33 (21 children)	-	Physical intervention; Large, flattened dummy with a hollow tube running through, gum shield and palatal training devices	20 participants had air bloat, 17 of these 20 swallowed air during breath-holding and 3 gulped air during hyperventilation.
Munakata 2008[100]	Longitudinal, Open Label	Costello syndrome; lissencephaly type 1	8	-	Physical intervention; Black Pepper Oil	Five of 8 participants showed increases in amount of oral intake, but need for enteral nutrition was not completely eliminated.

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Seguy 2002[101]	Retrospective Chart Review	SMA type I	3 with SMA;	-	Surgical intervention; Percutaneous endoscopic gastrostomy	Height and weight for age improved, but complication in children who had preexisting gastroesophageal reflux.
Sommer 1993[102]	Case Series, Retrospective Chart Review	De Lange syndrome	17 (16 children)	-	Describes trajectory or characteristics	13 participants had gastroesophageal reflux and also signs of the Sandifer complex.
Spiliopoulos 2012[103]	Retrospective Chart Review	Epidermolysis bullosa	19 (at least 5 children)	Simplified 0-4 dysphagia score	Surgical intervention; Fluoroscopically Guided Dilation of Esophageal Strictures	The mean dysphasia score improved significantly compared to baseline, but 5 pediatric patients suffered from nutritional failure and required gastronomy tube placement.
Stehr 2008[104]	Retrospective Chart Review	Epidermolysis bullosa	5	-	Surgical intervention; Non-endoscopic percutaneous gastrostomy	All patients tolerated gastronomy tube placement, with no perioperative complications.
Vowinkel 2014[105]	Case-series	Epidermolysis bullosa	12	-	Surgical intervention; Orthograde balloon dilation followed by retrograde dilation via the established gastrostomy	11 of the children showed improvement in growth and nutrition after a 24 month follow-up.
Zaffanello 2017[106]	Case-series	Achondroplasia	9	Sleep control test questionnaire	Describes trajectory or characteristics	78% had respiratory sleep disorder, but it was generally mild.
Sleep Disturbance / Disorders						

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Appleton 2012[107]	RCT	Undefined neuro-developmental disorders	146	Sleep diary, SCHQ, CSI, ESS, ABC	Pharmacologic intervention; Melatonin	Mean amount of sleep difference between placebo and melatonin was 22.43 minutes
Blankenburg 2003[108]	Tool / Scale Development	Specific Q3 conditions not reported	224	SNAKE, SDSC	Tool or scale development	SNAKE is a valid tool for diagnosing sleep disturbance in this population.
Boban 2015,[109] 2016[110]	Cross-sectional	Rett syndrome	364	SDSC, CSHQ	Describes trajectory or characteristics	Waking at night the most prevalent sleep problem in all children, affecting over 80%; while initiating and maintain sleep was most prevalent in younger children.
Braam 2008[111]	RCT	Chromosome 18q deletion, MPS III	51	Sleep diary	Pharmacologic intervention; Melatonin	Compared with placebo mean sleep onset time increased by 34 minutes, sleep latency decreased by 29 minutes, and total sleep time increased by 48 minutes
Bruni 1995[112]	Case control, Longitudinal	Tuberous sclerosis	10 + 10 healthy controls	Sleep diary	Describes trajectory or characteristics	Children with TS had shorter total sleep time, reduced sleep efficiency and more awakenings compared to controls.
Camfield 1996[113]	Case series	Undefined neuro-developmental disorders	6	Parent report of when child awake or asleep	Pharmacologic intervention; Melatonin	No notable difference in sleep pattern reported
Colville 1996[114]	Cross-sectional, Survey, Case series	MPSIII	80 (5 for intervention)	Questionnaire developed for study	Psychological intervention; Treatment goals set by a child psychologist, including set bedtime, if child awakes at night put back to bed firmly, set time allowed out of bed	Most treatment goals achieved in study period

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de Leersnyder 2011[115]	Open-label	Rett syndrome	88	Questionnaire developed for study	Pharmacologic intervention; Prolonged-Release Melatonin	Sleep latency decreased by 44%, sleep duration increased by 10.1%, number of awakenings decreased by 75%
Dodge 2001[116]	RCT	Unspecified developmental disabilities	20	Sleep diary	Pharmacologic intervention; Melatonin	Difference in sleep latency and duration of sleep not significantly greater than baseline.
Ellaway 2001[117]	Cross-sectional	Rett syndrome	83	Sleep diary	Describes trajectory or characteristics	Sleep characteristics did not change with age and did not show age related decreases in total and daytime sleep.
Evans 2016[118]	Cross-sectional	Mowat-Wilson syndrome	34	SDSC, DBC	Describes trajectory or characteristics	High level of sleep disturbance was found, with 44% scoring in the clinical disorder range; sleep disorders should be screened for in children with MWS.
Fraser 2002[119]	Survey	MPSIII	11 clinicians who treat MPSIII	-	Describes trajectory or characteristics	Sleep problems almost universal in this population and there is no single treatment that is viewed by all as beneficial.
Fraser 2005[120]	Cross-sectional, Survey	MPSIII	141 + 61 controls	Questionnaire validated for the study	Describes trajectory or characteristics	91.5% of children had sleep disturbance and melatonin and benzodiazepines were reported by parents as the most efficacious treatments.
Freeman 2016[121]	Cross-sectional	Smith-Lemli-Opitz syndrome	20	CSHQ	Describes trajectory or characteristics	Most markers of cholesterol synthesis defect severity were associated with severity of sleep disturbance.
Gringras 2012[122]	RCT	Unspecified Q3 conditions	146	Sleep diaries, CSDI, ABC, ESS	Pharmacologic intervention; Melatonin	Melatonin increased total sleep time and was most affective for children with the longest sleep latency.
Hancock 2005[123]	Case-control	Tuberous sclerosis	7 (6 children) + 21 healthy controls	-	Describes trajectory or characteristics	Normal patterns of melatonin excretion seen in TS patients who are responders to melatonin.

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Hancock 2005[124]	RCT	Tuberous sclerosis	7 (5 children)	Quine sleep index score, Sleep diary, Actigraphy	Pharmacologic intervention; Melatonin	No statistically significant improvements in sleep latency and sleep time on 10 mg of melatonin compared to 5 mg.
Hatonen 1999[125]	RCT	NCL3	3 + 2 with other types of NCL	Sleep log, wrist Actigraphy	Pharmacologic intervention; Melatonin	No change in activity rhythms resulting from melatonin, but families reported that sleep quality was slightly improved.
Heikkil 1995[126]	Cross-sectional	NCL3	7 + 15 with other types of NCL	Actigraphy	Describes trajectory or characteristics	In most patients sleep was fragmented and sleep phase was irregular.
Ingram 2017[127]	Cross-sectional	Agenesis of the corpus callosum	66	CSHQ	Describes trajectory or characteristics	78% of children had clinically significant sleep problems and children with more sleep problems had a worse quality of life.
Kirveskari 2000[128]	Cross-sectional	NCL3	28 (25 children) + healthy controls	Visual assessment of sleep	Describes trajectory or characteristics	In most patients the total sleep time and efficiency were significantly lower than in healthy controls.
Kirveskari 2001[129]	Case-series, Cross-sectional	NCL5	12 (at least 4 children)	Sleep Questionnaire, Actigraphy	Describes trajectory or characteristics	Patients under 20 years of age had excess of sleep at night and frequent daytime naps.
Laakso 1993[120]	Cross-sectional	Congenital hydrocephalus, Lennox-Gastaut syndrome, West syndrome	18 (10 children)	-	Describes trajectory or characteristics	More participants with LGS and sleep disturbance had disruptions in their temperature, cortisol or melatonin rhythms than LGS with normal sleep patterns.
Lehwald 2016[131]	Cross-sectional	NCL3	54	CSHQ	Describes trajectory or characteristics	96.3% had scores consistent with sleep disturbance; onset of sleep disturbance was associated with both onset of seizures and loss of vision.

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Lindblom 2006[132]	Cross-sectional	Aspartylglucosaminuria	81 (27 children) + 49 controls (23 children)	BNSQ	Describes trajectory or characteristics	61% of children with AGU reported daily sleep-related problems and showed more setting difficulties and snored more often than controls.
Maas 2008[133]	Cross-sectional	Jacobsen syndrome	43 (6 patients 18 years or older)	Adapted sleep questionnaire	Describes trajectory or characteristics	10 of the 43 participants had a sleep problem and 22 had a history of sleep problems.
Maas 2009[134]	Cross-sectional	Cri-du-chat	30 + 60 controls	Adapted sleep questionnaire	Describes trajectory or characteristics	Night waking problems, sleep disorder breath and poor-quality sleep more common in CDC compared to controls.
Maas 2011[135]	Tool / Scale Development	Rett syndrome, cri-du-chat, Jacobsen syndrome	345 (number of children with Q3 conditions unknown)	SQ-SP, CSI, SDSC	Tool or scale development	The SQ-SP is a valid tool for assessing sleep and sleep disturbance in this population.
Maas 2012[136]	Case-control	Cri-du-chat, Jacobsen syndrome	50 + 50 with other conditions	SQ-SP	Describes trajectory or characteristics	Snoring most prevalent sleep disturbance in CDC and JS, but no difference in severity of sleep problems between groups.
Mahon 2014[137]	Longitudinal, Survey	MPSIIIA, MPSIIIB	8 + 8 matched controls	CSHQ, Actigraphy, sleep diary	Describes trajectory or characteristics	Children with MPSIII have longer sleep latencies and greater daytime sleep compared to controls, but night sleep duration did not differ. In MPSIII, sleep efficiency declined and sleep latency increased with age.
McArthur 1998[138]	Longitudinal, RCT	Rett syndrome	9	Sleep diary, Actigraphy	Pharmacologic intervention; Melatonin	Melatonin decreased sleep latency and appeared to improve total sleep time and efficiency in patients who had the worse baseline sleep quality.

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Miyamoto 1999[139]	Case-series, Longitudinal	Rett syndrome	2	Sleep diary	Pharmacologic intervention; Melatonin	Melatonin improved sleep in both patients, and effect was maintained over 2 years without adverse effects.
Moser 2017[140]	Cross-sectional	Juvenile Huntington disease	33	Survey created for study	Describes trajectory or characteristics	87% of participants had disrupted sleep.
Mumford 2015[141]	Longitudinal	MPSIIIA, MPSIIIB	8 + 8 matched controls	Actigraphy	Describes trajectory or characteristics	MPS group showed significant fragmentation of circadian rhythm compared to controls.
Niakan 1979[142]	Case-series	Pelizaeus-Merzbacher disease	3	-	Describes trajectory or characteristics	Lower percentage of REM sleep seen than normal values.
O'Callaghan 1999[143]	Longitudinal, RCT	Tuberous sclerosis	7	Sleep diaries, Quine sleep index score	Pharmacologic intervention; Melatonin	Children treated with melatonin had a small improvement in total sleep time, but no effect on sleep fragmentation.
Phillips 2004[144]	Systematic review	Rett syndrome (and other ID)	-	-	Pharmacologic intervention; Melatonin	Melatonin treatment reduced time to sleep, but no significant effect on total sleep time, night awakenings and parental report.
Piazza 1990[145]	Cross-sectional	Rett syndrome	20	Momentary time sampling procedure	Describes trajectory or characteristics	RS girls had more total sleep, less night sleep and more daytime sleep than peers; night sleep was correlated with age.
Piazza 1991[146]	Case-series	Rett syndrome	3	Momentary time sampling procedure	Psychological intervention; Fading procedure	Intervention resulted in more regular sleep patterns by increasing night sleep and decreasing day sleep.
Rajan 2002[147]	Cross-sectional	De Lange syndrome	31 (19 children)	PSQ, PDSS, OSA18	Describes trajectory or characteristics	Children showed difficulties with falling asleep and staying asleep.
Ross 2002[148]	Open-label	Lennox-Gastaut syndrome, leukodystrophy, MPSII, MPSIII	46	Sleep diaries	Pharmacologic intervention; Melatonin	34 of the 46 patients showed improvement in sleep.

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Segawa 1990[149]	Cross-sectional	Rett syndrome	8	-	Describes trajectory or characteristics	The sleep-wake cycle is abnormal in RS.
Tietze 2014[150]	Cross-sectional, Tool / Scale Development	Unclear Q3 conditions	224	HOST, ESS, PSQI	Describes trajectory or characteristics, Tool or scale development	Sleep-related difficulties impact daily life of children and caregivers; the HOST is a valid tool for sleep-related difficulties.
Zambrelli 2016[151]	Cross-sectional	De Lange syndrome	46	SDSC	Describes trajectory or characteristics	Abnormal total sleep score for at least one SDSC factor found in 39% of participants and 15% had an abnormal total score.
Temperature Regulation						
Svedberg 2001[152]	Case-series	Smith-Lemli-Opitz syndrome, progressive encephaolopathia	6	Skin temperature measurements	Physical intervention; Acupuncture	3 children had a brief rise in temperature in the hand and one foot, with a tendency toward cumulative effect in additional sessions.
Svedberg 2005[153]	Case-control	Chromosome 22q11.2 deletion, SMA1	15 + 25 healthy controls	Infrared radiation to measure skin temperature	Describes trajectory or characteristics	Significant lower mean skin temperature in all measurement points compared to controls.
Tone and Motor Problems						
Abbruzzese 2016[154]	Case control	Cri-du-Chat	14 + 14 controls	-	Describes trajectory or characteristics	Participants with CdCS had more frequent and smaller steps than controls, but on average had a comparable gait speed.
Aberg 2001[155]	Open-label	NCL 3, NCL 6	16 + 5 controls	UPDRS	Pharmacological intervention; Levodopa or Selegiline	Mean UPDRS score decreased in the levodopa group
Air 2011[156]	Retrospective Chart Review	Glutaric acidemia type I, Lesch-Nyhan syndrome	31	BFMDRS, BADS, BPI, UPDRS	Deep Brain Stimulation	Those with secondary dystonia only had a small improvement in BFMDRS score 1 year later

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Beaulieu-Boire 2016[157]	Open Label	Ataxia telangectasia, MCM deficiency, NCL, Nemaline myopathy	11	BFMDRS	Surgical intervention; Deep Brain Stimulation	At one year follow-up Ataxia Telangectasia patient had deterioration of symptoms, Nemaline Myopathy patient had no change, and other patients had non-significant improvement
Boy 2015[158]	Cross-sectional	Glutaric acidemia type I	226	BADS	Describes trajectory or characteristics	BADS scores correlated with speed, but not test of stability or higher cognitive function.
Buizer 2017[159]	Retrospective Chart Review	Lipidoses	24	GMFCS, Caregiver Questionnaire, SPAT	Surgical intervention; Selective dorsal rhizotomy	Reduction in spasticity in legs, most reported improvements in dressing, washing and comfort
Bumin 2002[160]	Case Series	Rett syndrome	4	Number of stereotypical movements in 5 minutes of video, functional hand use (ability to eat a cracker) in 5 minutes of video	Physical intervention; Hand splints, elbow restraint	All subjects showed decrease in stereotypic behavior
Bürk 2009[161]	Tool / Scale Development	Friedrich's ataxia	96	SARA, FARS, ICARS	Describes trajectory or characteristics	SARA is valid and reliable to measure afferent ataxia in FA.
Cak 2014[162]	Case Series	NPC	3	-	Pharmacologic intervention; Imipramine	2 patients with cataplexy successfully treated
Cano 2005[163]	Tool / Scale Development	Friedrich's ataxia	77	ICARS	Tool or scale development	ICARS total score can be used to measure FA, but more studies are necessary to further test validity of all the subscales.
Carter 2010[164]	Cross-sectional	Rett syndrome	144	-	Describes trajectory or characteristics	Hand stereotypies seen in most subjects, with a median of 2 types stereotypies per subject but this decreased with age.

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Castelnau 2005[165]	Case Series	IND	6	BFMDRS	Surgical intervention; Pallidal Stimulation	Sustained decrease in dystonia in all patients and global motor improvement
Castilhos 2012[166]	Open label, Tool / Scale Development	MPS I, MPSIV, Adreno-myeloneuropathy, Mucolipidosis	38	SSPROM	Tool or scale development	SSPROM is a valid scale for children with progressive myelopathies secondary to inborn errors of the metabolism.
Corben 2010[167]	Longitudinal Study	Friedrich's ataxia	20	9HPT, BBT, JTHFT, FARS	Describes trajectory or characteristics	9HPT and BBT using the non-dominate hand can be used to show disease progression in FA.
Croarkin 2009[168]	Cross-sectional	Friedrich's ataxia	38	FARS	Describes trajectory or characteristics	FARS score is associated with gait velocity, stride length and cadence, and may be a useful screening tool
de Lattre 2013[169]	Tool / Scale Development, Prospective Cohort	SMA1	88 + 194 healthy controls	MFM	Tool or scale development	The MFM-20 can be used to assess motor function in young children with neuromuscular disease
Detweiler 2013[170]	Retrospective Chart Review	Costello syndrome	43	-	Describes trajectory or characteristics	Most children with Costello Syndrome have orthopedic manifestations and should be routinely referred to orthopedics.
Downs 2008[171]	Cross-sectional	Rett syndrome	99 (70 under 19 years)	Coding scheme developed for study	Describes trajectory or characteristics	General gross motor skills decline with age while complex motor skills do not.
Downs 2010[172]	Cross-sectional	Rett syndrome	144 (101 under 19 years of age)	WeeFIM, Hand Apraxia Scale, Level of hand function	Describes trajectory or characteristics	Hand function deteriorates with age and level of hand function is associated with the type of MECP2 mutation.

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Downs 2011[173]	Longitudinal	Rett syndrome	72 (54 under 19 years)	Hand Apraxia Scale, Level of hand function, ARSD Family Questionnaire	Describes trajectory or characteristics	Over time participants with RS and some grasping abilities lost skills, with those who were younger than 8 years more likely to lose skill.
Downs 2012[174]	Tool / Scale Development	Rett syndrome	12	StepWatch Activity Monitor, Rett Syndrome Gross Motor Scale	Tool or scale development	The StepWatch is an accurate tool to measure activity in RS, no matter the level of gross motor ability.
Downs 2015[175]	Tool / Scale Development	Rett syndrome	26	Actigraphs, Rett Syndrome Gross Motor Scale	Tool or scale development	The StepWatch is an accurate tool to measure activity in RS, no matter the level of gross motor ability.
Downs 2016[176]	Tool / Scale Development	Rett syndrome	293 (190 under 19 years)	RSGMS	Tool or scale development	The RSGMS may be a valid measure of gross motor skills in RS.
Downs 2017[177]	Cross-sectional	Rett syndrome	64	StepWatch Activity Monitor	Describes trajectory or characteristics	Adolescents led less active lives than children.
Dusing 2006[178]	Case-series	MPSI	4	Peabody Developmental Motor Scales	Describes trajectory or characteristics	There are early gross motor delays in MPSI and children with the condition should be referred to a physical therapist.
Dy 2017[179]	Tool/ Scale Development	Rett syndrome	24	Operational definitions of hand stereotypies	Tool or scale development	Achieved 50% level of agreement, so need more objective measures to evaluate hand stereotypies.
Elian 1996[180]	Cross-sectional	Rett syndrome	25	Unspecified questionnaire	Describes trajectory or characteristics	Hand movements are asymmetrical and appear to change with emotional or mental states.
Finkel 2008[181]	Tool/ Scale Development	SMA1	11	TIMP	Tool or scale development	The TIMP is a reliable measure of motor problems in SMA1.
FitzGerald 1990[182]	Longitudinal	Rett syndrome	32	Motor-Behavioral Assessment Scale	Describes trajectory or characteristics	The most common movement problems were stereotypy and gait disturbance.

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Foley 2011[183]	Longitudinal	Rett syndrome	77 (44 children)	RSGMS	Describes trajectory or characteristics	There is evidence of general stability in gross motor function over a 3 to 4 year period in girls and women with RS.
Freeman 2007[184]	Cross-sectional	IND	16 (6 children)	VABS, Adaptive Behavior Assessment Scale, Care and Comfort Hypertonicity Questionnaire	Describes trajectory or characteristics	There is variability in adaptive behavior functioning in this population.
Germanotta 2015[185]	Tool/ Scale Development	Friedrich's ataxia	14 + 18 control	SARA, InMotion Arm Robot	Tool or scale development	The InMotion Arm Robot was highly discriminative between subjects with FA and health controls.
Gimeno 2012[186]	Case-series, Tool/ Scale Development	Glutaric acidemia type I	5	BFMDRS, Canadian Occupational Performance Measure, Goal Attainment Scaling, CPCHILD questionnaire	Surgical intervention; Deep brain stimulation	No change in the BFMDRS after deep brain stimulation, which shows the limitations of impairment-focused measures.
Glanzman 2010[187]	Tool/ Scale Development	SMA1	26	CHOP INTEND	Tool or scale development	The CHOP INTEND is a reliable measure, but more validation is needed.
Glanzman 2011[188]	Tool/ Scale Development	SMA1	27	CHOP INTEND	Tool or scale development	The CHOP INTEND reflects disease severity measures.
Goldman 2012[189]	Case-control	Rett syndrome	20 with RS + 20 controls with autism	Coding system developed for hand stereotypies	Describes trajectory or characteristics	In RS the hand stereotypies are complex, continuous, at the body midline and involved mouthing, which is different from those seen in autism.

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Haddad 1997[190]	Cross-sectional	MLIII, MPSI, MPSII, MPSIII, MPSVI	48	Assessment of functional level - 5 item scale	Surgical and physical interventions; Surgery, physiotherapy, exercises	After early decompression functional improvement was seen with some benefit form simultaneous tendon release.
Hjartarson 2017[191]	Case-series	X-linked adrenoleukodystrophy	2	Modified Ashworth Scale	Pharmacologic interventions; Intrathecal baclofen	Intrathecal baclofen significantly reduced muscle tone.
Holloway 2006[192]	Systematic Review	IND	-	BFMDRS, UDRS, Abnormal Involuntary Movement Scale, Toronto Western Spasmodic Torticollis Rating, Tsui Scale for Cervical Dystonia, Truong and Fahn Myoclonus Scale	Surgical intervention; Deep brain stimulation	Mean changed in BFMDRS was 51.8%, with IND having no difference in outcomes in comparison to other dystonic etiology.
Humphreys 2016[193]	Cross-sectional	Rett syndrome	51 (at least 9 children)	RTT rigidity distribution score	Describes trajectory or characteristics	Rigidity found in 43 of 51 participants, starting as early as age 3 and started in the ankle region.
Ilg 2012[194]	Cohort study	Friedrich's ataxia	10 (7 children)	SARA, dynamic gait index, Activity-specific Balance Confidence Scale	Physical intervention; Video game-based coordinative training	Ataxia significantly reduced and balance improved after intervention.
Krosschell 2006[195]	Tool/ Scale Development	SMA1	44	HFMS	Tool or scale development	HFMS is a reliable and stable tool to assess motor function over a 6 month period.
Krosschell 2013[196]	Tool/ Scale Development	SMA1	38	TIMP	Tool or scale development	The TIMP is a reliable tool for assessing motor function in infants with SMA1.

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Kuhlen 2016[197]	Retrospective Chart Review	Chromosome 18q deletion, Lissencephaly Type 1, Metachromatic Leukodystrophy, NCL 3	16 (2 children)	-	Pharmacologic intervention; dronabinol	Improvements in severe treatment resistant spasticity in 12 patients.
Kwon 2011[198]	Longitudinal, Tool/ Scale Development	NCL3	82	UBDRS	Tool or scale development	The UBDRS is a valid tool for measuring clinical progression, including motor function.
Kyllerman 1994[199]	Case-series	Glutaric acidemia type I	12	-	Describes trajectory or characteristics	10 participants had severe dystonic-dyskinesia disorder, 1 had mild hyperkinetic disorder.
Iannaccone 1993[200]	Longitudinal	SMA1	58	Functional Motor Scale	Describes trajectory or characteristics	56% showed tongue fasciculation and 22% facial weakness.
Lim 2012[201]	Cross-sectional, Retrospective Chart Review	IND	12	BFMDRS	Surgical intervention; Pallidal deep brain stimulation	Outcome of deep brain stimulation is dependent on mutation.
Liow 2016[202]	Case-series, Longitudinal	IND	69	GMFCS, Dystonia Severity Assessment Plan, ICF-CY	Pharmacologic intervention; Gabapentin	Significant improvement in general muscle tone and involuntary muscle contractions.
Liu 2017[203]	Case-series	IND	3	BFMDRS	Surgical intervention; Subthalamic Nuclei Stimulation	BFMDRS scores improved in all a patients.
Lotan 2004[204]	Case-series, Longitudinal, N of 1	Rett syndrome	3	Rett Functional Evaluation Scale, RSGMS	Psychological intervention; Daily conductive educational program	Gross motor function improvements seen at the end of training.

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Lotan 2012[205]	Case-series, Longitudinal	Rett syndrome	4	Scale developed and validated for study	Physical intervention; Daily training program on a treadmill	General functional abilities improved considerably after training.
Mazzone 2014[206]	Longitudinal, Tool/ Scale Development	SMA1	74	HFMS, MFM	Tool or scale development	HMFS worked better in non-ambulant patients where the MFM worked better in very weaker patients.
Naganuma 1988[207]	Case-series, Longitudinal	Rett syndrome	3	Duration of stereotypic movements and duration of functional hand use	Physical intervention; Thumb abduction splints	Decrease in amount of time spent in stereotypic hand behavior and 1 patient had an increase in finger-feeding skills after hand splints.
Nava 2012[208]	Case-series	MPSII	2	-	Pharmacologic and physical interventions; Botulinum toxin type A, followed by serial casting and intensified physical therapy	Passive range of motion, muscle tone and gait performance improved significantly.
Nelson 2006[209]	Tool/ Scale Development	SMA1	40	GMFM	Tool or scale development	The GMFM is a valid tool in SMA.
Nissenkorn 2013[210]	Longitudinal, Open-label	Ataxia telangectasia	17	ICARS, UNDRS, AIMS	Pharmacologic intervention; Amantadine Sulfate	76.6% of participants had at least a 20% improvement in sum of all scales.
Nissenkorn 2016[211]	Tool/ Scale Development	Ataxia telangectasia	63	ICARS, SARA, Brief Ataxia Rating Scale	Tool or scale development	Both scales showed positive correlation between severity and age.

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Park 2016[212]	Retrospective Chart Review	IND	5 with IND	BFMDRS	Surgical intervention; Deep brain stimulation	Mean movement and disability scores decreased significantly at 60 month follow up.
Qvarfordt 2009[213]	Case-series, N of 1	Rett syndrome	3	Video analysis by coding system	Psychological intervention; Guided eating vs being fed	Guided eating improved mouth and spoon coordination, involvement in meal and cooperation in arm movements.
Sansare 2018[214]	Case-control	NPC	10 + 15 healthy controls	6-meter long electronic walkway, NIH NPC Neurologic Severity Scale, NeuroCom Balance SMART Equitest System, Kinematic assessment of the finger-to-nose test	Describes trajectory or characteristics	Participants showed significant deficits gait, balance and upper limb coordination.
Shaikh 2013[215]	Cross-sectional	Ataxia telangectasia	80 + 19 healthy controls	Accelerometer	Describes trajectory or characteristics	79 of 80 participants had abnormal involuntary movements and had both kinetic and postural tremor; 48 also had resting tremor.
Sharpe 1992[216]	N of 1	Rett syndrome	2	Stereotypic hand movements and hand-to-toy contact recorded in 10 second time samples	Physical intervention; Elbow orthosis and thumb abduction splints	Both subjects had a decrease in stereotypic hand movements and increase in toy contact with elbow orthosis, but not difference with thumb abduction splints.
Stahlhut 2017[217]	Tool/ Scale Development	Rett syndrome	42	Modified two-minute walk test, Rett syndrome specific functional mobility scale, RSGMS	Tool or scale development	Rett syndrome specific functional mobility scale and the modified two-minute walk test may be valid measures.

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Stasolla 2013[218]	Case-series	Rett syndrome	2	Measured intervals with stereotyped behavior and indices of happiness	Physical intervention; Wobble microswitch and optic sensors	Participants showed increase in performance, indices of happiness and decreased stereotyped movements.
Stasolla 2014[219]	Case-series	Rett syndrome	3	Number of items requested / chosen, Indices of happiness	Physical intervention; Picture exchange communication systems, Vocal output communication aid	Participants showed increase in requested and chosen items and indices of happiness.
Stasolla 2015[220]	Case-series	Rett syndrome	3	Measured intervals with stereotyped behavior and indices of happiness	Physical intervention; Assistive technology (photocells, interface and personal computer)	Participants showed increase in adaptive responses items and indices of happiness and decreased stereotyped movements.
Subramony 2005[221]	Tool/ Scale Development	Friedrich's ataxia	14	Friedrich's Ataxia Scale	Tool or scale development	Friedrich's Ataxia Scale may be a valid measure in FA.
Susatia 2010[222]	Tool/ Scale Development	Unspecified Q3 conditions	25 (4 children)	UDRS, BFMDRS	Tool or scale development, Surgical intervention; Deep brain stimulation	Blinded outcome assessments result in lower outcome scores and may be a more realistic assessment tool after deep brain stimulation.
Temuno 2007[223]	Cross-sectional	Rett syndrome	83	Pineda general severity scale	Describes trajectory or characteristics	RS participants with the MECP2 mutation showed more frequent hair pulling and more varied stereotypies.

First Author Year of Publication	Study Design	Q3 Condition(s)	Number of participants	Tools or Scales Used	Study Objective; Intervention(s)	Primary Outcome(s) / Conclusion(s)
Temudo 2008[224]	Cross-sectional	Rett syndrome	60	Pineda general severity scale, Motor-behavioral assessment scale	Describes trajectory or characteristics	Movement disorders in RS seem to reflect the rate of progression and severity of the syndrome.
Timmermann 2010[225]	Retrospective Chart Review	IND	23	BFMDRS, BADS	Surgical intervention; Bilateral pallidal stimulation	66.7% of patients showed improvement of 20% or better in severity of dystonia.
Tsering 2017[226]	Retrospective Chart Review	IND	4	BFMDRS, BADS	Surgical intervention; Deep brain stimulation	All participants experienced reductions in severity of dystonia.
Tuten 1989[227]	Case-series	Rett syndrome	2	Coding of videotapes of amount of stereotypic behavior	Physical intervention; Hand splints	No increase in feeding skills or hand wringing when splits where removed.
van Capelle 2012[228]	Tool/ Scale Development	Glycogen storage disease type II	91 (19 were 20 years or younger)	GMFM, Quick Motor Function Test	Tool or scale development	Quick Motor Function Test can reliably rate motor function in children with GSDII.
van Heest 1998[229]	Retrospective Chart Review	MPSI, MPSIII, MPSVI	22	Hand function questionnaire	Surgical intervention; Annular pulley release or Annular pulley release and partial flexor digitorum superficialis tendon resection	All patients had improved hand function.
Vasco 2016[230]	Case-control, Longitudinal	Friedrich's ataxia	11 + 13 controls	Gait analysis. SARA	Describes trajectory or characteristics	Gait analysis proved more sensitive measure of motor function than SARA.

First Author Year of Publication	Study Design	Q3 Condition(s)	Number of participants	Tools or Scales Used	Study Objective; Intervention(s)	Primary Outcome(s) / Conclusion(s)
Vignoli 2009[231]	Longitudinal	Rett syndrome	12 (7 children)	Stereotypies rated on a 1-3 scale	Describes trajectory or characteristics	Over time RS participants maintained stereotypies into adolescence.
Vuillerot 2012[232]	Longitudinal, Tool/ Scale Development	SMA1, Other unspecified Q3 conditions	152 (87 children)	Motor Function Measure	Tool or scale development	MFM showed good responsiveness, but needs to be validated.
Wales 2004[233]	Case-series	Rett syndrome	8	Videotaped, system of event coding used	Psychological intervention; Continuous adult attention vs no stimulation vs demands vs stimulation	Environmental conditions have limited effect on repetitive hand movements.
Wong 2017[234]	Cross-sectional	Rett syndrome	58	Stereotypies classification checklist from the literature	Describes trajectory or characteristics	Participants with atypical RS have more varied stereotypies; hair pulling, bruxism, retropulsion and protrusion of lips are more common in atypical RS.
Zannolli 2012[235]	RCT	Ataxia telangectasia	13	ICARS	Pharmacologic intervention; Betamethasone	Betamethasone reduced ICARS total score by a median of 16 points.
Zweije-Horman 1982[236]	RCT	NCL3	8	List of 30 observations of motor function, scored 1-5	Pharmacologic intervention; Orfenadrine, Amantadine, Madopar	None of the drugs led to a significant improvement in motor function.
Urinary Incontinence						
von Gontard 2001[237]	Case-control	SMA1	96 + 45 unaffected siblings + 59 healthy controls	CBC	Describes trajectory or characteristics	There is a high rate of urinary incontinence in this population that is often overlooked and not treated.

Table 2: Characteristics of included studies with multiple symptoms

First Author Year of Publication	Study Design	Symptom(s)	Q3 Condition(s)	Number of participants	Tools or Scales Used	Study Objective; Intervention(s)	Primary Outcome(s) / Conclusion(s)
Abraham 2015[238]	Cross-sectional	Feeding Difficulties, Tone and motor	Rett Syndrome	23	VDS, Penetration-Aspiration Scale	Describes trajectory or characteristics	Swallowing was disrupted by dysmotility of oral stage events, which was further compromised by recurrent dystonic and dyskinesia movements.
Ajay 2016[239]	Cross-sectional	Constipation, Urinary Incontinence	Glycogen storage disease type II	16	BCSS	Describes trajectory or characteristics	Daytime urinary incontinence and constipation was found in 6 of the 16 participants.
Ajmone 2014[240]	Cross-sectional	Behavioral, Tone and motor	De Lange syndrome	17	VABS, CBCL, CARS	Describes trajectory or characteristics	35% of participants had clinical scores in externalizing behavior and 30 % were borderline; participants show a 43 month delay in motor skills
Allen 2014[241]	Cross-sectional	Alertness, Behavioral	Chromosome 22q11.2 deletion	48	CBCL,SSRS	Describes trajectory or characteristics	Some association between family environment and parenting styles with social-behavioral outcomes.
Anderson 1992[242]	Cross-sectional	Alertness, Behavioral	Lesch-Nyhan syndrome	42	-	Describes trajectory or characteristics	All participants older than 5 had full alertness, 8 subjects over the age of 11 had talked about or attempted suicide.
Axelrad 2009[243]	Longitudinal study	Behavioral, Tone and motor	Costello syndrome	18	VMI, VABS	Describes trajectory or characteristics	Motor skills were mild in the range of disability; 56% had elevated externalizing scores and 6% had a clinically significant score.
Backman 2005[244]	Cross-sectional	Alertness, Behavioral	NC3	27	CBCL, TRF, CDI	Describes trajectory or characteristics	Most common behavior problems reported were social, thought, attention problems, somatic complaints and aggressive behavior.

First Author Year of Publication	Study Design	Symptom(s)	Q3 Condition(s)	Number of participants	Tools or Scales Used	Study Objective; Intervention(s)	Primary Outcome(s) / Conclusion(s)
Badaruddin 2007[245]	Cross-sectional	Alertness, Behavioral, Sleep Disturbance	Agenesis of the corpus callosum	61	CBCL	Describes trajectory or characteristics	Children with agenesis of the corpus callosum who are young were rated as having primarily problems with sleep, while older children were rated as having problems exceeded the cut-off on the scales for attention and aggressive behavior.
Barnes 2015[246]	Cross-sectional	Behavioral, Breathing Difficulties, Sleep Disturbance	Rett syndrome	74	RSBQ, ABC, CSS, VABS, CHQ, ADAMS	Describes trajectory or characteristics	Anxiety-like behavior is part of the phenotype but is inversely correlated to clinical severity; ADAMS is a valid tool to measure anxiety in Rett
Bax 1995[247]	Cross-sectional	Behavioral, Sleep Disturbance	MPSI, MPSII, MPSIII	258	Rutter's Parent Checklist	Describes trajectory or characteristics	High rates of behavioral problems reported, including destructiveness, restlessness and aggressiveness.
Beauchamp 2009[248]	Case series	Behavioral, Tone and motor	Glutaric acidemia type I	4	CBCL, MABC-2	Describes trajectory or characteristics	All patients had significant fine motor skills deficits; no behavioral concerns were reported
Berney 1999[249]	Cross-sectional	Behavioral, Constipation, Feeding difficulties, Sleep Disturbance, Tone and Motor Problems	De Lange syndrome	49	EAS Temperament Questionnaire, DOTS-R	Describes trajectory or characteristics	A variety of symptoms occurred frequently in this population, including hyperactivity, self-injury, aggression sleep disturbance, feeding difficulties and constipation.

First Author Year of Publication	Study Design	Symptom(s)	Q3 Condition(s)	Number of participants	Tools or Scales Used	Study Objective; Intervention(s)	Primary Outcome(s) / Conclusion(s)
Carotenuto 2013[250]	Case control	Breathing Difficulties, Sleep Disturbance, Tone and Motor Problems	Rett syndrome	13 + 40 controls	Periodic limb movement counted	Describes trajectory or characteristics	Rett participants in compared to controls showed increased rate of stage shifts and awakenings per hour, more periodic limb movement during sleep and a higher obstructive apnea index per hour.
Cass 2003[251]	Case series	Breathing Difficulties, Constipation, Feeding Difficulties, Sleep Disturbance	Rett syndrome	87	SOMA, Chailey Levels of Ability – Sitting, Drooling rated as none, mild, moderate or severe, Total breathing abnormality score 0-4	Describes trajectory or characteristics	Some symptoms improved, while other worsened with age, showing that Rett is not a degenerative condition.
Cialone 2012[252]	Survey	Behavioral, Tone and motor	NCL3	83	UBDRS	Describes trajectory or characteristics	Females with NCL Type 3 have a more severe disease course than males.
Cianfaglione 2015[253]	Cross-sectional, Survey	Behavioral, Breathing Difficulties, Tone and Motor Problems	Rett syndrome	91 + 66 in contrast group	Simplified severity score, RSBQ, VABS, Activity questionnaire, MIPQ, RBQ, CBCL	Describes trajectory or characteristics	Variable behavior problems reported may be associated with genetic mutation; hand stereotypies, breathing problems, sleep problems and anxiety or inappropriate fear reported commonly.

First Author Year of Publication	Study Design	Symptom(s)	Q3 Condition(s)	Number of participants	Tools or Scales Used	Study Objective; Intervention(s)	Primary Outcome(s) / Conclusion(s)
Cianfaglione 2015[254]	Cross-sectional, Survey	Breathing Difficulties, Constipation, Feeding Difficulties, Tone and Motor Problems	Rett syndrome	91+ 66 in contrast group	Simplified severity score, Health questionnaire, VABS	Describes trajectory or characteristics	Genetic mutation is associated with greater severity and epilepsy and weight, gastrointestinal, and bowel problems were commonly reported.
Cianfaglione 2016[255]	Systematic observation	Behavioral, Breathing Difficulties, Tone and Motor Problems	Rett syndrome	10 (6 children)	Simplified severity score, VABS, Behavioral categories created for study	Describes trajectory or characteristics	Hand stereotypies were independent of environment events, but self-injury may be related to adult attention.
Claro 2011[256]	Cross-sectional	Alertness, Sleep Disturbance	Cri-du-chat	116	ISQ-A	Describes trajectory or characteristics	Participants who showed high levels of fatigue were more likely to show high levels of autistic symptoms.
Collins 2002[257]	Cross-sectional	Behavioral, Tone and motor	Cri-du-chat	66	BPI	Describes trajectory or characteristics	Stereotyped behavior, self-injury and aggressive behavior were reported frequently in CDC
Cornish 1996[258]	Cross-sectional	Behavioral, Bowel Incontinence, Feeding Difficulties, Tone and Motor Problems, Urinary Incontinence	Cri-du-chat	27	Society for the Study of Behavioural Phenotypes Questionnaire	Describes trajectory or characteristics	The behavioral phenotype of CDC includes self-injury, repetitive movements, hypersensitivity to sound, clumsiness and obsessive attachment to objects.

First Author Year of Publication	Study Design	Symptom(s)	Q3 Condition(s)	Number of participants	Tools or Scales Used	Study Objective; Intervention(s)	Primary Outcome(s) / Conclusion(s)
Cross 2014[259]	Systematic Review	Behavioral, Tone and Motor Problems	MPSI, MPSII, MPSIIIA, MPSIIIB	1649	-	Describes trajectory or characteristics	Sleep disturbance is found in MPS III and challenging behavior is prevent in MPS II and III
Darling 2017[260]	Cross-sectional, Tool / Scale Development	Behavioral, Tone and Motor Problems	IND	47	PKANDRS	Tool or scale development	PKANDRS is a reliable and validated tool in this population
de Vries 2015[261]	Tool / Scale Development	Behavioral, Feeding Difficulties, Sleep Disturbance	Tuberous sclerosis	4	TAND Checklist, SDQ, Wessex Rating Scale	Tool or scale development	An outline of the TAND Checklist is presented.
Didden 2002[262]	Cross-sectional	Behavioral, Breathing Difficulties, Sleep Disturbance, Urinary Incontinence	Rett syndrome, Tuberous sclerosis	286 (6 with Q3 Conditions)	Modified sleep questionnaire developed for study, ABC	Describes trajectory or characteristics	Children with Intellectual Disability suffer from sleep problems, behavioral problems and urinary incontinence.
Fabio 2011[263]	Open-label	Alertness, Tone and Motor Problems	Rett syndrome	12 (2 children)	VABS, Videotaped observations	Physiological intervention; Selective attention training	Participants showed an increase in selective attention and decreased in amount of help needed.
Freeman 2008[264]	Retrospective Chart Review	Constipation, Feeding Difficulties	Epidermolysis bullosa	223	-	Describes trajectory or characteristics	GI problems were present in 58% of participants.

First Author Year of Publication	Study Design	Symptom(s)	Q3 Condition(s)	Number of participants	Tools or Scales Used	Study Objective; Intervention(s)	Primary Outcome(s) / Conclusion(s)
Fyfe 2007[265]	Tool / Scale Development	Feeding Difficulties, Tone and Motor Problems	Rett syndrome	97	Functional Ability Checklist, Filming and coding protocol	Tool or scale development	The filming and coding protocol may be a valid measure in RS.
Giesbers 2012[266]	Case-control	Bowel Incontinence, Urinary Incontinence	Rett syndrome	63 + 26 controls	Adapted incontinence questionnaire, VABS	Describes trajectory or characteristics	Urinary and fecal incontinence are common problems in RS and occur independent of age and level of adaptive functioning.
Glaze 1987[267]	Cross-sectional	Breathing Difficulties, Sleep Disturbance	Rett syndrome	11 + 36 controls	-	Describes trajectory or characteristics	Participants showed abnormal respiratory patterns during awake states and abnormal sleep patterns than controls.
Hall 2008[268]	Case-control	Behavioral Problems, Sleep Disturbance	De Lange syndrome	54 + 46 controls	CBI, ISQ	Describes trajectory or characteristics	Participants had more sleep problems than controls and were more likely to have self-injurious behavior if they had skin or eye problems.
Hawley 1985[269]	Cross-sectional	Behavioral Problems, Breathing Difficulties, Feeding Difficulties	De Lange syndrome	64	-	Describes trajectory or characteristics	The most frequent management problems in this condition include feeding problems, behavioral problems and respiratory tract infections.
Hecht 1991[270]	Cross-sectional	Sleep Disturbance, Tone and Motor Problems	Achondroplasia	13	Bayley Scales of Infant Development	Describes trajectory or characteristics	Participants showed delayed mortar development and frequent respiratory dysfunction.

First Author Year of Publication	Study Design	Symptom(s)	Q3 Condition(s)	Number of participants	Tools or Scales Used	Study Objective; Intervention(s)	Primary Outcome(s) / Conclusion(s)
Hunt 1993[271]	Cross-sectional	Behavioral Problems, Sleep Disturbance	Tuberous sclerosis	330	Unspecified questionnaire	Describes trajectory or characteristics	There is a high frequencies of hyperactive behavior and sleep problems in TS.
Hunt 1994[272]	Cross-sectional	Behavioral Problems, Sleep Disturbance	Tuberous sclerosis	40 + 59 controls	Developmentally Delayed Children's Behaviour Checklist, Sleep Index score	Describes trajectory or characteristics	Children with TS have a higher sleep disturbance and Total Behavior Problem scores than controls; there is a significant correlation between sleep and behaviors scores in TS.
Iturriaga 2006[273]	Retrospective Chart Review, Tool / Scale Development	Feeding Difficulties, Sleep Disturbance, Tone and Motor Problems	NPC	30 (27 children)	Disability scale created for study	Tool or scale development	Presents the age of detection of various symptoms depending on clinical form of NPC3.
Jamiolkowski 2016[274]	Cross-sectional	Alertness, Behavioral Problems, Bowel Incontinence, Feeding Difficulties, Sleep Disturbance, Urinary Incontinence	Glutaric aciduria type 1, Ornithine transcarbamylase deficiency, Propionic aciduria	152	PedsQL, Denver Developmental Screening Test, List of 33 items of possible behavioral and emotional problems	Describes trajectory or characteristics	Participants showed increased frequencies of behavioral and emotional problems.
Kawame 2003[275]	Retrospective Chart Review	Behavioral Problems, Feeding Difficulties	Costello syndrome	10	-	Describes trajectory or characteristics	All children showed significant irritability and sleep disturbance.

First Author Year of Publication	Study Design	Symptom(s)	Q3 Condition(s)	Number of participants	Tools or Scales Used	Study Objective; Intervention(s)	Primary Outcome(s) / Conclusion(s)
Kay-Rivest 2017[276]	Cross-sectional	Breathing Difficulties, Feeding Difficulties, Sleep Disturbance	Aicardi-Goutières syndrome, Krabbe disease, leukodystrophy, Pelizaeus-Merzbacher disease, x-linked adreno-leukodystrophy	12	Drool Quality of Life Assessment Questionnaire, Screening questionnaire with 23 common otolaryngology issues	Describes trajectory or characteristics	58% reported problems with drooling and had dysphagia and 0% reported sleep problems.
Lad 2017[277]	Cross-sectional	Bowel Incontinence, Urinary Incontinence	Friedrich's ataxia	59	SARA, Inventory of Non-Ataxic Symptoms, USP, NBD score, SF-Qualiveen Questionnaire	Describes trajectory or characteristics	80% reported lower urinary tract symptoms and 64% reported bowel symptoms.
Leighton 2001[278]	Cross-sectional	Breathing Difficulties, Sleep Disturbance	Galactosialidosis, MPSI, MPSII, MPSIII, MPSIIIA, MPSIIIB, MPSVI, MPSVII	26	Sleep diary	Describes trajectory or characteristics	OSA was present in 24 patients and frequent awakenings and poor sleep quality were found in several patients.
Mizuno 1974[279]	Case-series	Behavioral Problems, Tone and Motor Problems	Lesch-Nyhan syndrome	4	Self-mutilation graded on scale of 0-5, Dystonia graded on scale of 0-5	Pharmacologic intervention; L-5-Hydroxytryptophan or L-tryptophan or L-Dopa	L-5-Hydroxytryptophan decreased self-injury but did not reduce choreoathetosis.
Mordekar 2017[280]	Retrospective Chart Review	Constipation, Feeding Difficulties, Tone and Motor Problems	Rett syndrome, MPSIII, West syndrome	12	-	Pharmacologic intervention; Parenteral nutrition	Use of parenteral nutrition improved dystonia, GERD and intestinal dysmotility.

First Author Year of Publication	Study Design	Symptom(s)	Q3 Condition(s)	Number of participants	Tools or Scales Used	Study Objective; Intervention(s)	Primary Outcome(s) / Conclusion(s)
Moss 2009[281]	Cross-sectional, Survey	Behavioral Problems, Tone and Motor Problems	Cri-du-chat, De Lange syndrome	741 + 56 with unspecified ID	RBQ, Wessex Scale, Autism Screening Questionnaire	Describes trajectory or characteristics	CDC has a unique profile of repetitive behavior.
Motil 2012[282]	Cross-sectional, Survey	Constipation, Feeding Difficulties	Rett syndrome	983	Questionnaire developed for study	Describes trajectory or characteristics	Gastrointestinal dysmotility and chewing and swallowing difficulties are common symptoms in RS.
Mount 2002[283]	Tool / Scale Development	Behavioral Problems, Breathing Difficulties, Sleep Disturbance, Tone and Motor Problems	Rett syndrome	143 + 85 controls with profound ID	RSBQ, Physical ability scales	Tool or scale development	The RSBQ can distinguish between the RS and controls but needs to be validated.
Nag 2017[284]	Cross-sectional, Survey	Behavioral Problems, Sleep Disturbance, Tone and Motor Problems	Chromosome 4p Deletion	10 (6 children)	Structured observation, VADS, CBCL, CSHQ, Social Communication Questionnaire	Describes trajectory or characteristics	Patients may have a better motor skill outcome than previously described, but sleep problems persist into adulthood.
Nidiffer 1983[285]	Survey	Behavioral Problems, Feeding Difficulties, Urinary Incontinence	MPSII	30	Questionnaire developed for study	Describes trajectory or characteristics	Hyperactivity, sleep problems, physical aggression occur frequently in children with MPSIII and may be part of the syndrome.

First Author Year of Publication	Study Design	Symptom(s)	Q3 Condition(s)	Number of participants	Tools or Scales Used	Study Objective; Intervention(s)	Primary Outcome(s) / Conclusion(s)
Niemczyk 2017[286]	Cross-sectional	Constipation, Behavioral Problems, Bowel Incontinence, Urinary Incontinence	Mowat-Wilson syndrome	47	Parental Questionnaire: Enuresis/Urinary Incontinence, Developmental Behaviour Checklist	Describes trajectory or characteristics	97% of participants had urinary incontinence and 81.4% had fecal incontinence; 46.2% of children and 25% of teens exceeded the clinical cut-off for behavioral problems.
Piazza 1993[287]	Case-series	Feeding Difficulties, Tone and Motor Problems	Rett syndrome	5	Scoring developed for study	Psychological intervention; Training in scooping food, bringing food to mouth, and placing spoon in mouth by a trainer	All girls with RS showed improvement in their scooping abilities, ability to bring spoon to mouth and ability to self-feed.
Quest 2014[288]	Case-series	Behavioral Problems, Tone and Motor Problems	Rett syndrome	5	Coding system developed for study	Describes trajectory or characteristics	Negative affect more likely to occur in stressful conditions, while hand stereotypy did not differ with stressful conditions.
Schretlen 2005[289]	Cross-sectional	Alertness, Behavioral Problems	Lesch-Nyhan syndrome	33 + 11 healthy controls	CBC, Adaptive Behavior Scale	Describes trajectory or characteristics	Participants showed self-injury, aggression and distractibility.
Senirili 2016[290]	Case-series	Feeding Difficulties, Tone and Motor Problems	NPC	16	Penetration and Aspiration scale	Describes trajectory or characteristics	75% of participants had postural imbalance and 12.5% had some degree of dysphagia.

First Author Year of Publication	Study Design	Symptom(s)	Q3 Condition(s)	Number of participants	Tools or Scales Used	Study Objective; Intervention(s)	Primary Outcome(s) / Conclusion(s)
Stavinoha 2011[291]	Cross-sectional	Breathing Difficulties, Sleep Disturbance	De Lange syndrome	22	PSQ, PDSS, OSA18	Describes trajectory or characteristics	Sleep disordered breathing and sleepiness are common in DLS.
Thurm 2016[292]	Case-series	Behavior, Tone and Motor Problems	Smith-Lemli-Opitz syndrome	33	VABC, Autism Diagnostic Observation Schedule	Describes trajectory or characteristics	Developmental milestone were delayed and aggressive behavior found in almost half of participants.
Ucar 2010[293]	Open-label	Behavioral Problems, Sleep Disturbance	MPSIIIA	12	T-DSM-IV-S, Clinic Global Impression Scale - Severity	Pharmacologic intervention; Risperidone	Best improvement found in hyperactivity, followed by opposition/ defiance subscales; sleep disturbance improved in 6 patients.
Visser 2011[294]	Case-series, Open-label	Behavioral Problems, Tone and Motor Problems	Lesch-Nyhan Syndrome	5	BFMDRS, questionnaire developed for severity of self-injurious behaviors	Pharmacologic intervention; Levodopa-Dopa or carbidopa	All patients discontinued levodopa due to worsening of motor function or lack of effect.

List of abbreviations:

9HPT - 9-Hole Peg Test

ABC - Aberrant Behaviour Checklist

ADAMS - Anxiety, Depression, and Mood Scale

AIMS - Abnormal Involuntary Movement Scale

BADS - Barry-Albright Dystonia Scale

BASC – Behavior Assessment System for Children

BBT – Box and Block Test

BCSS – Bladder Control Symptom Score

BFMDRS - Burke-Fahn-Marsden Dystonia Rating Scale

BNSQ - Basic Nordic Sleep Questionnaire

BPI - Behavior Problems Inventory

CAPND - Clinical Assessment of Paediatric Neurogenic Dysphagia

CARS - Childhood Autism Rating Scale

CBC - Compulsive Behavior Checklist

CBCL - Child Behavior Checklist

CBI - Challenging Behaviour Interview

CDC - Cri-du-chat

CDI – Children's Depression Inventory

CHOP INTEND - The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

CHQ - Child Health Questionnaire

CPAP - Continuous positive airway pressure

CPRS - Conners' Parent Rating Scale

CSDI – C1omposite Sleep Disturbance Index

CSHQ - Children's Sleep Habits Questionnaire

CSI - Composite Sleep Disturbance Index

CSS - Clinical Severity Scale

DASH - Diagnostic Assessment for the Severely Handicapped

DOSS - The Dysphagia Outcome Severity Scale

DOTS-R – Dimensions of Temperament Questionnaire

DPC-P - Developmental Behaviour Checklist-Primary Care

DSFS - Drooling Severity and Frequency Scale

ECBI - Eyberg Child Behaviour Inventory

ESS- Epworth Sleepiness Scale

ESS-C - Epworth Sleepiness Scale - Children

FARS - Friedreich's Ataxia Rating Scale

FDA - Frenchay Dysarthria Assessment

GMFCS - Gross Motor Function Classification System

GMFM - Gross Motor Function Measure

HMFS - Hammersmith Functional Motor Scale

HOST - Holistic assessment of sleep and daily troubles

ICARS - International Cooperative Ataxia Rating Scale

ICF-CY - WHO International Classification of Functioning, Disability and Health, Children & Youth version

IND -Infantile neuroaxonal dystrophy

ISQ - Infant Sleep Questionnaire

ISQ-A - Adapted Infant Sleep Questionnaire

JTHFT - Jebsen Hand Function Test

LRSQ - Liverpool Respiratory Symptom Questionnaire

MABC-2 - Movement Assessment Battery for Children

MCM deficiency - Methylmalonyl-CoA Mutase deficiency

MFM – Motor Function Measure

MIPQ - Mood, Interest and Pleasure Questionnaire

mMRC Dyspnea Scale - Modified Medical Research Council Dyspnea Scale

MPII - Mucolipidosis type II

MPIII - Mucolipidosis type III

MPS – Mucopolysaccharidosis

MPSI - Mucopolysaccharidosis type I

MPSII - Mucopolysaccharidosis type II

MPSIII - Mucopolysaccharidosis type III

MPSVI - Mucopolysaccharidosis type VI

MPSVII - Mucopolysaccharidosis type VII

MSAS - Memorial Symptom Assessment Scale

NBD Score - Neurogenic Bowel Dysfunction Score

NCBRF - Nisonger Child Behavior Rating Form

NCL - Neuronal ceroid lipofuscinosis

NCL3 - Neuronal ceroid lipofuscinosis type 3

NCL6 - Neuronal ceroid lipofuscinosis type 6

NPC - Niemann–Pick Type C

OSA - obstructive sleep apnea

PDSS - Pediatric Daytime Sleepiness Scale

PKANDRS - PKAN-Disease Rating Scale

PSQ - Pediatric Sleep Questionnaire

RBQ - Repetitive Behaviour Questionnaire

RS - Rett syndrome

RSBQ - Rett Syndrome Behavior Questionnaire

RSGMS - Rett Syndrome Gross Motor Scale

SARA - Scale for the Assessment and Rating of Ataxia

SBRS - Sanfilippo Behaviour Rating Scale

SDQ – Strengths and Difficulties Questionnaire

SDSC - Sleep Disturbance Scale for Children

SIB – Self-injurious behaviour

SIB-R - Scales of Independent Behavior – Revised

SMA1 - Spinal Muscular Atrophy Type 1

SNAKE - Schlaffragebogen für Kinder mit Neurologischen und Anderen Komplexen Erkrankungen

SOMA - Schedule for Oral Motor Assessment

SPAT - Spasticity Assessment Test

SQ-SP – Sleep Questionnaire

SSPROM - Severity Score System for Progressive Myelopathy

SSRS – Social Skills and Problem Behavior Rating System

T-DSM-IV-S - Turgay DSM IV Based Child and Adolescent Behavior Disorders Screening and Rating Scale

TEA-CH - Test of Everyday Attention for Children

TEF - The Mental and Physical Trait Energy and Fatigue Scales

TIMP - Test of Infant Motor Performance

TRF – Teacher Report Form

UBDRS - Unified Batten Disease Rating Scale

UDRS – Unfired Dystonia Rating Scale

UPDRS - Unified Parkinson Disease Rating Scale

USP - Urinary Symptom Profile

VABC - Vineland Adaptive Behavior Composite

VABS - Vineland Adaptive Behavior Scales

VDS - Videofluoroscopic Dysphagia Scale

VMI - The Beery Developmental Test of Visual-Motor Integration

WeeFIM - Functional Independence Measure for Children

Y-BOCS - Yale-Brown Obsessive Compulsive Scale

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