ORIGINAL RESEARCH

Determinants of quality of life in Rett syndrome: new findings on associations with genotype

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ABSTRACT

Background Rett syndrome is a genetically caused neurodevelopmental disorder associated with functional deficits and comorbidities. This study investigated relationships between genotype, functional abilities and comorbidities and quality of life in Rett syndrome.

Methods The International Rett Syndrome Database, InterRett, was used as a sampling frame for this observational study. Information was collected to describe functional abilities (walking and feeding), health (Sleep Disorder Scale for Children, the Rett Syndrome Behavioural Questionnaire), parental health (12-item Short Form Health Survey) sociodemographic factors (parental employment and education) and quality of life (Quality of Life Inventory-Disability) for 210 individuals with Rett syndrome. Univariate and multivariate regressions were used to analyse the relationships between the independent variables and quality of life.

Results Compared with individuals with the p.Arg270* mutation, those with the p.Arg294* mutation type had the poorest quality of life (coeff −12.81, 95% CI −23.49 to 2.12), despite this being recognised as a clinically milder genotype. Overall better walking and feeding skills and seizure parameters were more associated with better quality of life and poor sleep and behavioural difficulties with poorer quality of life.

Conclusions These findings suggest that genotype, functioning and health each have implications for quality of life and should be considered when counselling families and planning clinical and support management strategies.

INTRODUCTION

Rett syndrome (MIM:312750) is a rare neurodevelopmental disorder affecting approximately 1 in 9000 live female births.[1] The condition is characterised by largely normal early development followed by a regression of acquired hand and communication skills. It is defined by four main criteria: loss of hand skills, loss of communication skills, hand stereotypies and gait abnormalities.[2]

Caused by a mutation in the X-linked *MECP2* gene,[3] Rett syndrome is a severe life-limiting disorder[4] with impacts on multiple body systems[5–7] as well as being associated with severe functional impairment. The clinical spectrum is broad and varied and closely linked to the underlying genotype.[8–10] Those with the p.Arg133Cys, p.Arg306Cys and p.Arg294* mutations or C-terminal deletions are generally milder in severity than those with the p.Arg106Trp, p.Arg168*, p.Arg255*, p.Arg270* mutations.[8 9] Individuals with milder mutations generally perform better in terms of functional outcomes such as hand use and mobility[8] and those with the p.Arg133Cys mutation are most likely to have verbal skills.[11]

Epilepsy is diagnosed in around 80% of individuals and can range in severity according to age of onset, drug responsiveness and seizure semiology.[5 12–14] Sleep disturbances, with night waking, night laughing and screaming being distinctive features, also affect a similar proportion, though in general the prevalence decreases with age.[15] Lower respiratory tract infection was identified as the most common cause of death in our Australian population-based longitudinal dataset[4] although in an international sample, only one in five had been admitted to hospital on this account in the previous 5 years.[16] Growth retardation is a common feature with one in three having a gastrostomy placement usually because of feeding difficulties or inadequate weight gain.[17] Longitudinal data demonstrated that nutritional status appears to improve postgastrostomy but there was no evidence of improvement in other outcomes such as episodes of illness or time spent in hospital or of any positive impact on parental physical or mental well-being.[17]

Parental well-being has been investigated both cross-sectionally[18] and longitudinally[19] in Australia. The child having frequent sleep or behavioural disturbances, as measured by appropriate domains of the Rett Syndrome Behaviour Questionnaire[20] and the type of *MECP2* gene mutation were each associated with later poorer parental physical well-being while the child having enteral feeding was associated with later poorer emotional well-being.[19] Because of the multiple impacts of Rett syndrome both on those affected and their family, the quality of life (QOL) of both groups is a developing area of research.[21]

The WHO defines QOL as a "broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment".[22] Principles for the measurement of QOL particularly in the context of intellectual disability have indeed been proposed.[23] These include the following: involving the degree to which people have life experiences that they value; reflecting domains that contribute to a full and interconnected life; considering the context of physical, social and cultural environments that are important to people and including measured experiences both common to all humans and those unique to individuals.[23] Based on extensive qualitative data, the Quality of Life Inventory-Disability

(QI-Disability) comprises six domains that are consistent with these principles.[23] These are physical health, positive emotions, negative emotions, social interaction, leisure and the outdoors and independence.[24] Thus, this current study aimed to assess QOL in Rett syndrome employing QI-Disability which has been validated for children and adults affected by this disorder.[24–26] Factors such as age, mutation type, health and functioning were investigated for their impact on QOL, adjusting for family factors including socioeconomic status.

METHODS

Data source

The International Rett Syndrome Phenotype Database (InterRett) was established in 2002 to create a central database for Rett syndrome.[27] Families of cases registered with the database who had participated in a 2015 follow-up study[7 28] which required them to be English-speaking and for their child to have a pathogenic *MECP2* mutation, were telephoned and recruited to a 2018 follow-up study. The questionnaire inquired about aspects of health, QOL and parental well-being. The questionnaire was administered mainly online using REDCap (Research Electronic Data Capture) software.[29] Paper questionnaires were administered to four families.

Independent variables

Mutations were grouped as C-terminal deletion, early truncating, large deletion, p.Arg106Trp, p.Arg133Cys, p.Arg168*, p.Arg255*, p.Arg270*, p.Arg294*, p.Arg306Cys and p.Thr158Met, and all other pathogenic mutations were grouped as 'other'. Current age was categorised as 'younger than 12 years', '12–18 years', '19–28 years' or 'older than 28 years'. Mobility was categorised as follows: 'unable to walk', 'walks with assistance' and 'walks with no assistance on most surfaces'. Feeding pattern was separated as: 'full tube feeding', 'partial oral and tube feeding' and 'full oral feeding'. Seizure frequency over the previous 12 months was categorised as: 'not controlled (daily/more than once a day)', 'occasionally (once per month or week)', 'completely under control (at most twice a year)' and 'no epilepsy diagnosis'. Antibiotic use for respiratory infection over the last 12 months was grouped by the responses: '2 or more times', 'once' and 'not at all'.

The Sleep Disorder Scale for Children (SDSC) is a validated measure for reporting sleep problems in children.[30] The SDSC comprises 26 items that are rated on a five-point Likert scale and group into six subscales. The disorders of initiating and maintaining sleep (DIMS) and the disorders of excessive somnolence (DOES) subscales were used for the current study. Each subscale was scored through the summation of all the subscale items. The scores were then compared with the normative data reported in the initial validation paper[30] as follows. Each score was subtracted from the mean subscale score divided by the SD of the normative DIMS or DOES dataset to calculate a z-score. The z-score was then transformed to a t-score by multiplying by 10 and adding 50. The t-score was dichotomised as: scores within normal range ('below 70') and scores outside of normal range ('70 and above').

The Rett Syndrome Behavioural Questionnaire (RSBQ)[20] was included in the questionnaire. The RSBQ comprises 45 items which are rated on a three-point Likert scale and group into eight subscales. For the purposes of this study, general mood (eight items, total possible score=16), breathing problems (five items, total possible score=10), fear/anxiety (four items, total possible score=8) and total score (45 items, total possible score=90) were included in the analytic models.

Parental employment was grouped by the combined employment status of the mother and father. It was categorised as: 'both full-time', 'one full-time one part-time', 'one full-time one homemaker', 'at least one retired' and the rest of combinations were grouped as 'other'. Highest education level achieved by the mother was categorised as 'university degree', 'trade/technical certificate' or 'secondary school and below' and other responses where the biological mother was not known were assigned to a 'missing' category.

The 12-item Short Form Health Survey (SF-12) was included in the questionnaire to assess the health outcomes of the person answering the questionnaire[31] The SF-12 has two subscales: Physical Component Summary (PCS) and Mental Component Summary (MCS) which assess the physical and mental well-being, respectively, of the person answering the questionnaire.

Dependent variable

The domains of QOL for adults with Rett syndrome have been found to be similar to those for children with Rett syndrome.[26] Therefore, QI-Disability, a validated measure for QOL in children with intellectual disability including individuals with Rett syndrome[24] was considered appropriate to assess QOL for all individuals with Rett Syndrome in this study. The measure comprises 32 items that are rated on a five-point Likert scale and group into six subscales: physical health, positive emotions, negative emotions, social interactions, independence and leisure and outdoors. Following transformation to a 100-point scale, item scores in each subscale were summed and divided by the number of items to give a subscale score. The mean of the six subscale scores was calculated to give the total QOL score.

Statistical analyses

Descriptive statistics were used to characterise the study variables and describe their distributions. Univariate and multivariate linear regression models were used to estimate the relationship between the dependent and independent variables. Three multivariate models were developed characterised by the inclusion of (1) age, mutation types and socioeconomic variables, (2) age, health, function and socioeconomic variables and (3) age, mutation type, health, function and socioeconomic variables. Estimates and their CIs were reported. Missing data were considered to be missing at random. Data were analysed using Stata 15.1 (Stata, College Station, Texas, USA).

RESULTS

Child and family characteristics

Questionnaires were administered to families of 232 individuals with a confirmed pathogenic *MECP2* mutation with 215 returning a completed questionnaire. The 210 subjects whose parents returned the questionnaire and for whom full mutation details were available formed the study case group. The questionnaire was completed mostly by the natural mother (87.1%) followed by the natural father (9.1%) and in a small minority by other family members. Most (n=199, 94.8%) individuals lived in the parental home and the remainder lived in a group home or community residential unit.

Frequency distributions by age groups, mutation types, mobility, feeding patterns, seizure frequency over the last 12 months, antibiotic use for respiratory infection over the last 12 months, parental employment, mother highest education, and sleep t-scores are shown in table 1. The age of the individual

Table 1 Characteristics of individuals with Rett syndrome (n=210)

Variable	Level	N (%)
Age groups	12 and younger	33 (15.7)
	12–18 years	87 (41.4)
	19–28 years	52 (24.8)
	28 and older	38 (18.1)
Mutation types	p.Arg270*	11 (5.2)
	C-terminal deletion	19 (9.1)
	Early truncating	14 (6.7)
	Large deletion	14 (6.7)
	p.Arg106Trp	11 (5.2)
	p.Arg133Cys	16 (7.6)
	p.Arg168*	26 (12.4)
	p.Arg255*	29 (13.8)
	p.Arg294*	14 (6.7)
	p.Arg306Cys	12 (5.7)
	p.Thr158Met	22 (10.5)
	Other	22 (10.5)
Mobility	Unable to walk	71 (33.8)
	Walks with assistance	65 (30.95)
	Walks with no assistance on most surfaces	72 (34.3)
	Missing	2 (0.95)
Constipation	Present with moderate or major impact	97 (46.2)
	Present with no or minor impact	86 (41.0)
	Absent	26 (12.4)
	Missing	1 (0.5)
Feeding patterns	Full tube feeding	41 (19.5)
	Partial oral and tube feeding	60 (28.6)
	Full oral feeding	108 (51.4)
	Missing	1 (0.5)
Seizure frequency over the last 12 months	Not controlled (daily/more than once a day)	27 (12.9)
	Occasionally (once per month or week)	68 (32.4)
	Completely under control (at most twice a year)	55 (26.2)
	No epilepsy	60 (28.6)
Antibiotic use frequency for respiratory infection over the last 12 months	Two or more times	29 (13.8)
	Once	46 (21.9)
	Not at all	134 (63.8)
	Missing	1 (0.5)
DIMS† t-score	70 and above	55 (26.2)
	Below 70	150 (71.4)
	Missing	5 (2.4)
DOES‡ t-score	70 and above	37 (17.6)
	Below 70	164 (78.1)
	Missing	9 (4.3)
	Variable	Mean (SD)
RSBQ§ (n=210)	General mood	4.9 (3.9)
	Breathing problems	3.8 (3.1)
	Fear/anxiety	3.1 (2.0)
	Total score	32.8 (13.6)
SF-12¶ (n=210)	Physical Component Summary	50.1 (9.4)
	Mental Component Summary	44.7 (9.0)
Variable	Values	N (%)
Parental employment	Both full-time employed	60 (28.6)
	One full-time and one homemaker	60 (28.6)
	One full-time and one part-time	37 (17.6)
	Other	31 (14.8)
	At least one retired	22 (10.5)
Mother highest education	University degree	130 (61.9)
	Trade/Technical certificate	29 (13.8)
	Secondary school	47 (23.4)
	Missing	4 (1.9)

*P-value < 0.05
†Disorders initiating and maintaining sleep
‡Disorders of excessive somnolence
§Rett Syndrome Behavioural Questionnaire
¶12-item Short Form Survey

with Rett syndrome at questionnaire completion range from 6 to 51 years (median 18 years and 2 months). About two fifths (41.4%) were aged 12–18 years and a quarter (24.8%) in the 19–28 years group. Among the mutation types, the most prevalent were p.Arg255* (13.8%) and p.Arg168* (12.4%) while the p.Arg106Trp (5.2%), p.Arg270* (5.2%) and p.Arg306Cys (5.7%) were less frequent (table 1).

A third (34.3%) of the individuals could walk independently, slightly fewer than a third (30.95%) could walk but only with assistance, and the remainder (33.8%) could not walk. Just over half (51.4%) were eating orally, more than quarter (28.6%) had a combination of oral and enteral feeding and less than one-fifth (19.5%) were completely reliant on enteral nutrition. Nearly three quarters (71.5%) had a diagnosis of epilepsy, but of these, only a few had very frequent seizures. More than a third (35.7%) had been treated with antibiotics for a respiratory infection in the past 12 months but only a small group (13.8%) had received them two or more times and more than a fifth (21.9%) only once in the past 12 months. For sleep disturbances, slightly more than a quarter (26.2%) had a DIMS subscale t-score≥70 and less than one-fifth (17.6%) had a DOES subscale score ≥70, respectively, indicating sleep dysfunction while just over two thirds (71.4%) had a DIMS subscale t-score and 78.1% a DOES subscale score below 70 within the normal range (table 1).

In more than one quarter (28.6%) of families, both parents were working full-time and a similar proportion (28.6%) had one full-time parent while the other was a homemaker. Less than one-fifth (17.6%) had one parents working full-time and the other part-time, 10.5% had at least one retired parent and in 14.8% there were other combinations of working arrangements. More than half (61.9%) of the mothers had a university degree, 13.8% the equivalent of a trade/technical certificate and 23.4% only completed high school (table 1).

The text below describes the final multivariate model unless otherwise stated.

Associations between age group and QOL

Compared with children younger than 12 years, total QOL score was lower for each of the older age groups: teenage children (−6.38, 95% CI −11.08 to 0.95), young adults (−6.46, 95% CI −12.60 to −0.33) and adults 28 years and older (−6.62, 95% CI −14.15 to 0.91) (table 2). Differences in QOL by age group were not apparent for the physical health or positive emotions domains (online supplementary tables 1 and 2). Compared with children younger than 12 years, the negative emotion score was

Table 2 Relationships between independent variables and total quality of life scores

		Univariate				Model 1		Model 2		Model 3		
		N	Mean (SD)	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value	N	Coefficient (95% CI)	P value
Age group	12 and younger	33	71.75 (14.49)							33		
	12–18 years	87	69.81 (13.55)	−1.94 (−7.45 to 3.58)	0.489	−2.84 (−8.37 to 2.70)	0.313	−5.89 (-11.17 to 0.61)	0.029*	81	−6.38 (-11.80 to 0.95)	0.022*
	19–28 years	52	70.17 (13)	−1.57 (−7.58 to 4.43)	0.606	−1.56 (−7.64 to 4.51)	0.612	−6.28 (-12.38 to 0.18)	0.044	48	−6.46 (-12.60 to 0.33)	0.039*
	28 and older	38	68.51 (14.15)	−3.24 (−9.65 to 3.18)	0.321	−2.51 (−10.01 to 4.98)	0.509	−6.11 (−13.47 to 1.24)	0.103	33	−6.62 (−14.15 to 0.91)	0.084
Mutation type	p.Arg270*	11	67.56 (14.79)							10		
	C-terminal deletion	19	72.97 (17.28)	5.41 (−4.67 to 15.49)	0.292	2.82 (−7.39 to 13.02)	0.587			18	−2.45 (−12.73 to 7.83)	0.638
	Early truncating	14	75.45 (16.49)	7.88 (−2.84 to 18.60)	0.149	6.95 (−3.61 to 17.51)	0.196			14	−1.72 (−12.17 to 8.74)	0.746
	Large deletion	14	69.44 (12.46)	1.87 (−8.85 to 12.59)	0.731	1.99 (−8.63 to 12.60)	0.712			11	−1.42 (−12.41 to 9.56)	0.798
	Other	22	68.98 (11.58)	1.41 (−8.41 to 11.24)	0.777	1.24 (−8.50 to 10.98)	0.801			22	−5.73 (−15.34 to 3.89)	0.241
	p.Arg106Trp	11	75.87 (14.05)	8.30 (−3.04 to 19.65)	0.150	8.57 (−2.73 to 19.87)	0.136			9	1.78 (−9.72 to 13.27)	0.760
	p.Arg133Cys	16	73.23 (14)	5.66 (−4.76 to 16.08)	0.285	5.43 (−4.84 to 15.70)	0.298			15	−4.58 (−15.41 to 6.25)	0.405
	p.Arg168*	26	70.06 (9.68)	2.49 (−7.07 to 12.06)	0.608	3.42 (−6.06 to 12.90)	0.478			24	1.41 (−8.12 to 10.94)	0.771
	p.Arg255*	29	67.41 (13.43)	−0.15 (−9.57 to 9.27)	0.975	−0.84 (−10.25 to 8.56)	0.860			26	−4.04 (−13.39 to 5.32)	0.395
	p.Arg294*	14	60.46 (12.45)	−7.11 (−17.83 to 3.61)	0.193	−6.48 (−17.00 to 4.03)	0.226			13	−12.81 (-23.49 to 2.12)	0.019*
	p.Arg306Cys	12	70.56 (13.13)	3.00 (−8.11 to 14.10)	0.595	1.73 (−9.30 to 12.76)	0.757			12	−8.07 (−19.01 to 2.88)	0.147
	p.Thr158Met	22	70.11 (13.62)	2.55 (−7.28 to 12.37)	0.610	0.77 (−8.98 to 10.53)	0.876			21	−4.40 (−14.09 to 5.30)	0.371
Mobility	Unable to walk	71	65.51 (13.7)							67		
	Walks with assistance	65	71.51 (12.62)	6.00 (1.49 to 10.52)	0.009*			7.12 (2.60 to 11.65)	0.002*	61	7.35 (2.76 to 11.93)	0.002*
	Walks with no assistance on most surfaces	72	72.76 (13.6)	7.24 (2.85 to 11.64)	0.001*			7.34 (2.44 to 12.24)	0.004*	67	8.47 (3.38 to 13.57)	0.001*
Constipation	Present with moderate or major impact	97	67.82 (12.54)							90		
	Present with no or minor impact	88	72.06 (14.50)	4.24 (0.29 to 8.19)	0.035*			2.29 (−1.65 to 6.23)	0.252	80	1.97 (−2.07 to 6.00)	0.337
	Absent	26	71.56 (13.77)	3.74 (−2.15 to 9.63)	0.212			1.20 (−4.71 to 7.11)	0.689	25	1.56 (−4.46 to 7.59)	0.609
Feeding patterns	Full tube feeding	41	62.44 (13.34)							37		
	Partial oral and tube feeding	60	71.55 (12.76)	9.11 (3.90 to 14.33)	0.001*			7.79 (2.13 to 13.45)	0.007*	55	9.64 (3.74 to 15.53)	0.002*
	Full oral feeding	108	72.17 (13.13)	9.74 (5.01 to 14.46)	<0.001*			5.39 (−0.13 to 10.91)	0.056	103	6.86 (1.18 to 12.54)	0.018*

Continued

Table 2 Continued

		Univariate				Model 1		Model 2		Model 3		
		N	Mean (SD)	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value	N	Coefficient (95% CI)	P value
Seizure frequency over the last 12 months	Not controlled (daily/more than once a day)	27	63.69 (14.89)							23		
	Occasionally (once per month or week)	68	69.59 (15.03)	5.90 (−0.14 to 11.94)	0.055			5.81 (−0.23 to 11.83)	0.059	64	4.54 (−1.68 to 10.76)	0.152
	Completely under control (at most twice a year)	55	71.87 (10.79)	8.18 (1.94 to 14.41)	0.010*			6.63 (0.33 to 12.92)	0.039*	52	5.42 (−0.99 to 11.83)	0.097
	No epilepsy	60	71.49 (13.11)	7.80 (1.65 to 13.95)	0.013*			5.42 (−0.80 to 11.64)	0.087	56	5.45 (−0.90 to 11.79)	0.092
Antibiotic use frequency for respiratory infection over the last 12 months	Two or more times	29	64.79 (15.62)							26		
	Once	46	68.49 (12.02)	3.70 (−2.55 to 9.95)	0.244			−0.43 (−6.74 to 5.88)	0.893	43	0.11 (−6.24 to 6.47)	0.972
	Not at all	134	71.78 (13.3)	6.99 (1.59 to 12.39)	0.011*			0.35 (−5.71 to 6.41)	0.909	126	0.71 (−5.47 to 6.88)	0.821
DIMS t-score†	70 and above	55	66.62 (13.85)							50		
	Below 70	150	71.69 (13.03)	5.07 (0.95 to 9.19)	0.016*			1.57 (−2.78 to 5.92)	0.477	145	1.49 (−2.94 to 5.92)	0.507
DOES‡ t-score	70 and above	37	63.12 (11.71)							33		
	Below 70	164	72.06 (13.45)	8.94 (4.22 to 13.66)	<0.001*			1.71 (−3.61 to 7.03)	0.527	162	1.82 (−3.68 to 7.32)	0.514
RSBQ§	General mood	210	4.89 (3.9)	−0.92 (−1.38 to 0.46)	<0.001*			−0.55 (−1.35 to 0.25)	0.179	195	−0.37 (−1.18 to 0.45)	0.372
	Breathing problems	210	3.8 (3.06)	−0.30 (−0.91 to 0.31)	0.328			0.61 (−0.23 to 1.44)	0.153	195	0.63 (−0.21 to 1.46)	0.139
	Fear/Anxiety	210	3.1 (2.01)	−1.32 (−2.23 to 0.41)	0.005			0.03 (−1.14 to 1.20)	0.963	195	0.34 (−0.86 to 1.53)	0.580
	Total score	210	32.8 (13.64)	−0.31 (−0.44 to 0.18)	<0.001*			−0.30 (−0.61 to 0.00)	0.053	195	−0.36 (−0.67 to 0.05)	0.023*
SF-12¶	Physical Component Summary	210	50.09 (9.42)	0.14 (−0.05 to 0.34)	0.156	0.08 (−0.14 to 0.29)	0.478	−0.06 (−0.27 to 0.15)	0.559	195	−0.02 (−0.24 to 0.19)	0.820
	Mental Component Summary	210	44.75 (9.04)	0.39 (0.19 to 0.59)	<0.001*	0.41 (0.20 to 0.62)	<0.001*	0.29 (0.09 to 0.49)	0.004*	195	0.28 (0.07 to 0.48)	0.008*
Parental employment	Both full-time employed	60	69.45 (14.49)							55		
	One full-time and one homemaker	60	70.3 (13.29)	0.85 (−4.05 to 5.75)	0.733	1.60 (−3.39 to 6.58)	0.528	2.21 (−2.40 to 6.81)	0.346	56	1.49 (−3.32 to 6.31)	0.540
	One full-time and one part-time	37	73.41 (11.19)	3.96 (−1.65 to 9.58)	0.165	4.25 (−1.50 to 9.99)	0.146	3.70 (−1.56 to 8.96)	0.167	34	2.61 (−2.89 to 8.11)	0.349
	Other	31	67.62 (16.6)	−1.83 (−7.76 to 4.11)	0.545	−2.33 (−8.76 to 4.10)	0.475	−1.60 (−7.47 to 4.27)	0.592	30	−2.75 (−8.78 to 3.29)	0.370
	At least one retired	22	68.01 (10.75)	−1.44 (−8.14 to 5.25)	0.671	−2.71 (−10.39 to 4.97)	0.488	−1.54 (−8.84 to 5.76)	0.678	20	−2.86 (−10.32 to 4.61)	0.451
Mother education	University degree	130	70.26 (13)							119		
	Trade/Technical certificate	29	71.53 (12.57)	1.27 (−4.26 to 6.79)	0.652	2.83 (−2.76 to 8.41)	0.319	3.65 (−1.53 to 8.83)	0.166	28	4.01 (−1.19 to 9.20)	0.130
	Secondary school	47	67.86 (15.48)	−2.40 (−6.98 to 2.18)	0.303	−0.62 (−5.59 to 4.35)	0.807	0.37 (−4.32 to 5.06)	0.877	44	1.44 (−3.32 to 6.20)	0.552
	Missing	4	74.09 (19.54)	3.83 (−9.83 to 17.49)	0.581	2.62 (−11.30 to 16.54)	0.710	1.40 (−10.93 to 13.74)	0.822	4	2.33 (−10.39 to 15.06)	0.717

*P<0.05
†Disorders initiating and maintaining sleep.
‡Disorders of excessive somnolence
§Rett Syndrome Behavioural Questionnaire
¶12-item Short Form Survey.

similar for teenagers and adults to 28 years old but scores were higher indicating less challenging behaviours for adults older than 28 years (6.74, 95% CI 0.02 to 13.46) (online supplementary table 3). Compared with those aged 12 years and younger, scores for the independence domain were lower for each older age group, particularly adults 28 years and older (−23.44, 95% CI −35.82 to 11.06) (online supplementary table 4). Teenage children scored the lowest in the leisure and outdoors domain (−10.10, 95% CI −20.08 to 1.94) and young adults scored the lowest in the social interaction domain (−10.25, 95% CI −20.50 to 0.0) (online supplementary tables 5 and 6).

Genotype on QOL

Relative to those with the p.Arg270* mutation, those with the p.Arg294* group had the lowest total QOL score coefficient at −12.81 (95% CI −23.49 to 2.12) with the p.Arg306Cys also low (−8.07, 95% CI −19.01 to 2.88). For individuals with the p.Arg294* mutation, this pattern was reflected across most of the QOL domains with low scores in the physical health (−16.68, 95% CI −28.04 to 5.31) and positive emotions (−23.49, 95% CI −40.11 to 6.87) domains (online supplementary tables 1 and 2). p.Arg294* scores for the negative emotion domain were low in the univariate analysis (−13.92, 95% CI −25.9 to 1.94) but the effect reduced when adjusted for age, health functioning and socioeconomic factors (−2.17, 95% CI −11.71 to 7.36) (online supplementary table 3). Independence (−12.24, 95% CI −29.81 to 5.33), leisure and outdoors (−10.21, 95% CI −29.26 to 8.83) and social interactions (−11.89, 95% CI −29.75 to 5.98) domains scores were also low compared with the reference group which was those with the p.Arg270* mutation (online supplementary table 4–6). Otherwise, those with the p.Arg306Cys, p.Thr158Met and the p.Arg168* mutations also had low scores for the positive emotions domain (online supplementary table 2). We also observed that those with the p.Arg270* had generally higher scores for the positive emotion and leisure and outdoors domains.

Walking/feeding and QOL

Relative to those who were unable to walk, adjusted total QOL scores were higher for those who could walk without (8.47, 95% CI 3.38 to 13.57) or with (7.35, 95% CI 2.76 to 11.93) assistance (table 2). For each domain, except for negative emotions, the same pattern for each group was seen (online supplementary tables 1–6). Those who could walk without assistance had better scores for the physical health (6.17, 95% CI 0.75 to 11.59) and independence (19.85, 95% CI 11.48 to 28.22) domains compared those unable to walk.

Compared with the group receiving total enteral feeding, those who feed entirely orally had higher total QOL scores (6.86, 95% CI 1.18 to 12.54) and the group with combined enteral and oral feeding had even higher total scores (9.64, 95% CI 3.74 to 15.53) (table 2). Higher domain scores were also found in the physical health (8.79, 95% CI 2.52 to 15.06), positive emotion (12.31, 95% CI 3.14 to 21.47) and independence (10.65, 95% CI 0.97 to 20.34) domains for those using mixed feeding methods. Leisure and outdoors domain scores were higher for both oral feeding groups compared with those who were fully enterally fed.

Comorbidities and QOL

Compared with the group who experienced uncontrolled seizures, those who experienced occasional seizures had higher total QOL scores (4.54, 95% CI −1.68 to 10.76) with slightly higher scores again for those whose seizures were controlled (5.42, 95% CI −0.99 to 11.83) and those with no diagnosis of epilepsy (5.45, 95% CI −0.90 to 11.79). This same pattern was reflected by each group in the physical health and positive emotions domains (online supplementary tables 1 and 2). Those with no epilepsy diagnosis had higher physical health (6.62, 95% CI −0.12 to 13.37) and positive emotions (17.50, 95% CI 7.64 to 27.37) domain scores (online supplementary tables 1 and 2).

There were no remarkable differences in the groups according to frequency of use of antibiotics for respiratory infection. Compared with individuals with constipation that had moderate to major impact, QOL scores were slightly higher for those with constipation and less impact (1.97, 95% CI −2.07 to 6.00) and those without constipation (1.56, 95% CI −4.46 to 7.59).

In the univariate analysis, total QOL scores were higher for those with a t-score below 70 compared with those with a t-score above 70 for the DIMS (5.07, 95% CI 0.95 to 9.19) and DOES (8.94, 95% CI 4.22 to 13.66) sleep subscales (table 2). These results were attenuated when age, mutation type, health, functioning and socioeconomic variables were accounted for (table 2). However, there were still higher physical health domain scores for those with t-score below 70 in both the DIMS (6.20, 95% CI 1.48 to 10.91) and DOES (10.66, 95% CI 4.81 to 16.51) subscales, after accounting for the effects of the other covariates (online supplementary table 1).

For each point increase in the RSBQ indicating greater clinical severity, total QOL scores reduced on average by 0.36 points (95% CI –0.67 to 0.05). For every increase in point for the fear/anxiety subscale, there was a 1.52 (95% CI -2.59 to 0.45) point reduction in the negative emotions domain score but a 2.26 (95% CI 0.29 to 4.23) increase in the independence domain score (online supplementary tables 3 and 4). For each increase in the general mood subscale indicating poorer mood, there was a −2.38 (95% CI –3.11 to 1.66) reduction in the negative emotions domain score (online supplementary table 3).

Parental variables and child QOL

For the SF-12, each point increase in the MCS was associated with a 0.28 (95% CI 0.07 to 0.48) point increase for the total QOL score (table 2). This same pattern was found in the physical health (0.22, 95% CI 0.0 to 0.43), positive emotions (0.34, 95% CI 0.03 to 0.66), independence (0.33, 95% CI 0.0 to 0.66) and leisure and outdoors (0.42, 95% CI 0.06 to 0.78) domains. For the PCS subscale, there was a 0.14 (95% CI −0.08 to 0.37) increase in the physical health domain and a 0.22 (95% CI −0.57 to 0.13) decrease in the independence domain.

There were no remarkable differences between the groups of combined parental employment status.

Relative to the children of mothers who had completed a university degree, the children of those who have completed a trade/technical certificate had a 4.01 (95% CI −1.19 to 9.20) increase in the total QOL score. This same increase was seen in the positive emotions (6.35, 95% CI −1.73 to 14.43) and independence (8.46, 95% CI −0.08 to 17.0) domains for the trade/technical certificate group.

DISCUSSION

The most striking finding in this study was that girls and women with the p.Arg294* mutation tended to have the poorest QOL overall and in each of the domains. QOL was also poorer in those over 12 years relative to those under the age of 12 years. Better health parameters in relation to epilepsy and sleep disturbance and functioning in relation to walking and eating ability

were generally associated with better QOL outcomes. Higher scores for parental mental well-being were associated with small increases in QOL in some domains.

Given that those with the p.Arg294* mutation generally have a relatively mild phenotype with an increased likelihood of independent walking,[8] our genotype results might at first seem unexpected. Nevertheless, they are consistent with the findings from a US health-related QOL study where this was the mutation with the lowest psychosocial summary score.[32] Also, in keeping with our current findings, an earlier study using the Australian population-based database found that mood disturbances and night time behaviours were also most common in those with this mutation.[33] Two other studies supported the evidence for more sleep disturbances including more problems initiating and maintaining sleep in those with a p.Arg294* mutation.[15 28] In our current study, sleep disturbance was also associated with poorer total QOL, an effect which was much attenuated, as might be expected, after adjustment for genotype, although still associated with an effect in the physical health QOL domain. Overall increased symptoms of mood disturbance, fear and anxiety, as determined using the RSBQ,[20] were associated with poorer QOL although this effect, as might be expected, were also attenuated after adjustment for genotype. While depression is difficult to measure and poorly understood in Rett syndrome, symptoms of anxiety have sometimes been identified.[34–36] Taken in combination, these findings suggest that in contrast to the apparently mild clinical severity, there is a behaviour phenotype which includes sleep disturbance that is associated with poor QOL for those with the p.Arg294* mutation.

Despite our findings relating to the p.Arg294* mutation, in general, those unable to walk had poorer outcomes in most domains relative to those who could walk independently or walk with assistance. This would be consistent with previous relationships seen with aspects of clinical severity[10] as well as qualitative research where parents reported that their daughters derived pleasure from being ambulant.[25] Similarly, those who were fully dependent on enteral feeding had poorer QOL outcomes than those who could eat orally. If feeding difficulties necessitate gastrostomy insertion, encouraging oral feeding where there is capacity to do so seems to be associated with greater child QOL while still supporting the caregiver for the delivery of everyday food, fluids and medications. Constipation occurs commonly in conditions such as Rett syndrome[37 38] but we did not find that its presence or severity were related to QOL. We also found that a lower seizure frequency was associated with better QOL in most domains. Epilepsy is a common symptom of Rett syndrome and is associated with clinical severity.[39] Seizure onset and frequency vary by age as well as by genotype.[5 13 14 39] Over half of 200 French families with a child with Rett syndrome reported that their daughter's seizures were a major problem and a third a moderate problem for their 'health-related QOL'.[40] Drug-resistant epilepsy which can be problematic in Rett syndrome[4] was also a concern for these families.[40] Thus, it will be important to consider QOL in the evaluation of any new therapeutic initiatives that are introduced, particularly for epilepsy. After adjusting for genotype, functioning and health status still had some important relationships with QOL.

Health-related QOL is a different but related concept to QOL[41] and focuses mainly on functional status and health outcomes rather than aspects of social well-being and the individual's environment. However, there were some consistencies between the findings from ours and a US study[32] where a generic instrument not specifically applicable to children with severe intellectual disability.[42] The psychosocial summary scores were highest (best QOL) for those with the most severe mutations like p.Arg270*, p.Arg255* and p.Arg106Trp and lowest for p.Arg294* which is comparatively a much milder mutation. Conversely for the physical summary scores, the effects were generally reversed with mild mutations like p.Arg133Cys and Arg306Cys having higher scores while p.Arg270* and p.Arg255* had much lower physical summary scores. Their findings for the psychosocial summary by genotype were similar to our fully adjusted results for total QOL. However, we measured the fuller concept of QOL and showed, for example, that ability to walk was associated with higher total QOL and social interaction domain scores.

Rather than measuring health-related QOL[41] which relates strongly to capacity for functioning, we elected to measure the related but different concept of QOL using a measure validated for Rett syndrome.[24] Our research took advantage of the InterRett database to recruit an accessible sample of families for the study.[27] A large sample size is important in investigating rare disorders such as Rett syndrome to provide better characterised age groups and mutation types as well as other clinical features. In contrast to many studies in this disorder which mainly focus on children, the longevity of the InterRett database[43 44] allowed for representation of much older age groups. We have been able to provide novel information on the QOL outcomes for this population including adulthood. We however acknowledge that the results of this study can be affected by survival bias as those with better clinical outcomes will have higher chance of survival.[4] Our questionnaire included a comprehensive range of variables which were incorporated into our analysis, including health, functioning, behavioural, parental well-being and socioeconomic status variables. These variables being collated in a multivariate model allowed us to disentangle the determinants of QOL in Rett syndrome.

CONCLUSION

This study offers novel information on the determinants of QOL in Rett syndrome and gives insight into possible clinically relevant targets for improving QOL. For the first time, we have been able to demonstrate that genotype appears to have important implications for QOL. Given the heterogeneity in symptomatology in this disorder, this is important new knowledge that needs to be considered during the counselling and management processes to ensure that every child and family is provided with the appropriate support.

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Contributors JM was responsible for the analysis and interpretation of data, drafting the work and revising it critically for important intellectual content. JD was responsible for the conception and design of the work, analysis and interpretation of data, drafting the work and revising it critically for important intellectual content. KW was responsible for analysis and interpretation of data and revising it critically for important intellectual content. HL was responsible for acquisition and interpretation of data, drafting the work and revising it critically for important intellectual content. JD is responsible for the overall content as guarantor.

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