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The natural history of scoliosis in females with Rett syndrome

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Conflicts of Interest:

The authors have no conflicts of interest to declare.

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Ethics approvals for data access were obtained from the Princess Margaret Hospital for Children, Western Australia; Royal Perth Hospital, Perth; Women's and Children's Hospital, South Australia; Royal Children's Hospital, Melbourne; Monash Medical Centre, Melbourne; Sydney Children's Hospitals Network, Sydney; Mater Health Services, Brisbane; and Royal Children's Hospital, Brisbane.

Level of evidence: Level 4

Abstract

Study Design – Population-based longitudinal observational study.

Objectives – To describe the prevalence of scoliosis in Rett syndrome, structural characteristics and progression, taking into account the influences of age, genotype and ambulatory status.

Summary of Background Data – Scoliosis is the most common orthopaedic comorbidity in Rett syndrome yet very little is known about its natural history and influencing factors such as age, genotype and ambulatory status.

Methods – The infrastructure of the Australian Rett Syndrome Database was used to identify all cases with confirmed Rett syndrome in Australia and collect data on genotype and walking status. We identified radiological records from children's hospitals throughout Australia and those records held at home and described the Cobb angle of each curve. Time to event analysis was used to estimate the median age of onset of scoliosis and the log-rank test to compare by mutation type. Latent class group analysis was used to identify groups for the trajectory of walking status over time and a multilevel linear model used to assess trajectories of scoliosis development by mutation type and walking status. We used a logistic regression model to estimate the probability of developing a scoliosis with a Cobb angle $>60^\circ$ at 16 years in relation to Cobb angle and walking status at 10 years of age.

Results – The median age of scoliosis onset was 11 years with earliest onset in those with a p.Arg255* mutation or large deletion. Scoliosis was progressive for all mutation types except for those with the p.Arg306Cys mutation. Scoliosis progression was reduced when there was capacity to walk independently or with assistance. Cobb angle and walking ability at age 10 can be reliably used to identify those who will develop a very severe scoliosis by age 16.

Conclusions – These data on prognosis of scoliosis inform clinical decision making about the likelihood of progression to very severe scoliosis and the need for surgical management.

Keywords - epidemiology, Rett syndrome, scoliosis, natural history, scoliosis progression, spine deformity

KEY POINTS

1. Scoliosis is the most common orthopaedic comorbidity in Rett syndrome and occurs in 50% of cases by the age of 11 years.
2. Scoliosis is usually progressive except when occurring in those with the p.Arg306Cys mutation.
3. Progression is reduced when the child maintains the capacity to walk either independently or with assistance.
4. A Cobb angle $<25^{\circ}$ at the age of 10 years in conjunction with the ability to walk independently reduces the risk of very severe scoliosis (Cobb angle $>60^{\circ}$) at the age of 16 years by 86%.

MINI ABSTRACT

Scoliosis occurred in 50% of the population with Rett syndrome by 11 years and was usually progressive except when associated with the p.Arg306Cys mutation. Progression was reduced when walking skills were maintained. Cobb angle and walking at 10 years predicted the risk of a Cobb angle $>60^{\circ}$ by age 16 years.

INTRODUCTION

Rett syndrome is a neurodevelopmental disorder that predominantly affects approximately one in 9000 live female births¹ and is caused by a mutation in the MECP2 gene.² Early developmental milestones are generally normal followed by a period of developmental regression at around 6 to 30 months of age. At this time, hand function and/or communication skills are lost, and there is development of hand stereotypies and impaired gait.³ The disability is severe and those affected have severely affected functional abilities and comorbidities such as poor growth,⁴ breathing abnormalities,⁵ epilepsy,⁶ sleep difficulties,⁷ and scoliosis.^{8,9}

Neurological impairments including hypotonia are apparent during early childhood with hypertonia and rigidity sometimes developing in adulthood.¹⁰ These impairments can be asymmetrical.¹¹ Scoliosis is the most common orthopaedic complication in Rett syndrome and has been shown previously to be present in approximately 75% of a population-based cohort by age 13 years (n=231).⁸ Learning to walk and the presence of the p.Arg294* mutation were found to be protective of developing scoliosis⁸; findings replicated in a large U.S. clinical study.⁹

There are limited data on the progression of scoliosis in Rett syndrome although two earlier case series found that the curve may progress at approximately 15° per year.^{12,13} These studies were poorly powered (n=12 and n=41) and the samples were not representative of the variability in Rett syndrome now understood since the discovery of its genetic cause. The trajectory of scoliosis has been the topic of two studies of children with severe cerebral palsy.^{14,15} In 110 children, age was a strong predictor of Cobb angle, particularly in children with a tracheostomy and a Cobb angle of 40° prior to the age of 12 years indicated that progression was likely.¹⁴ In 37 institutionalized children with cerebral palsy, scoliosis was more severe with poor function and progression to a severe scoliosis more likely if the Cobb angle reached 40° prior to age 15 years.¹⁵

In Rett syndrome, factors that potentially influence the progression of scoliosis include genotype and ambulatory status. Previous studies have found relationships between genotype and clinical severity¹⁶ and specific comorbidities,^{6,8,17} and longitudinal trajectories of sleep disturbances.⁷ Functional abilities are variable. During early

development, most girls learn to sit and approximately half learn to walk.¹⁸ The course of Rett syndrome was originally conceptualized in four stages although this has never been validated in prospective population-based studies. The last of the stages was named the “late motor deterioration phase” during which time the ability to walk is lost.¹⁰ However, some individuals maintain the ability to walk through adulthood.¹⁹ Ambulatory status, namely walking, could have an association with the development of deformity including scoliosis.

The Australian Rett Syndrome Database (ARSD) was established in 1993 and is a population-based registry with information collected from clinicians and families longitudinally.^{20,21} This allows comprehensive investigation of the natural history of scoliosis in Rett syndrome, which can inform an optimal monitoring plan and support timely family counselling as to whether spinal fusion would be an appropriate management. Our primary objectives for the current study were to (1) describe the structural characteristics of scoliosis in Rett syndrome; (2) examine the trajectories of scoliosis, taking into account the influences of age, genotype, and ambulation status; and (3) identify predictors of progressive and very severe scoliosis. Our secondary objective was to replicate previous published analyses of the likelihood of scoliosis developing in Rett syndrome using our larger current dataset.

METHODS

All females in the registry with clinically³ or genetically confirmed Rett syndrome were included in this study. Families/carers of females registered in the ARSD were invited to complete an initial questionnaire at the time of registration since the database was established in 1993 and also to participate in up to six follow-up surveys administered since 2000.⁷ From existing data, information was collected on genotype, age at scoliosis onset, having learned to walk, and later ambulation status. Mutations were grouped as large deletions (LD), C-terminal deletions (CT), early truncating (ET), p.Arg106Trp, p.Arg133Cys, p.Arg168*, p.Arg255*, p.Arg270*, p.Arg294*, p.Arg306Cys and p.Thr158Met mutations. All others mutations were grouped as “other”. Age at scoliosis onset was defined as the age when scoliosis was first diagnosed (Cobb angle > 10°) or first recorded in the database or medical records (if age at diagnosis not available). Learned to walk was coded as independent walking or otherwise as indicated in the initial

family questionnaire. Ambulation status was also categorised as either walking independently, able to walk with assistance, or unable to walk, at each of the follow-up questionnaires. Using up to six observation points, latent class growth modeling was used to identify groups of individuals with different patterns of ambulation over time. The ambulation status at 10 years was identified from the longitudinal dataset and if data were not available the family of the child was contacted to ascertain status at that age. A binary variable was created to indicate very severe scoliosis (a Cobb angle $>60^\circ$) at 16 years present if (1) the girl reached that level of curvature before 16 years, (2) the interpolated Cobb angle, calculated using a linear function involving the square rooted Cobb angle and age at the data point prior to and after 16 years, was higher than 60° at 16 years, or (3) if the girl underwent spinal fusion surgery before age 16 years.

From the questionnaire administered in 2009, or from the initial family questionnaire for cases recruited during 2010, we ascertained (A) scoliosis had not been diagnosed; (B) scoliosis had been diagnosed but there had been no surgical intervention; or (C) scoliosis surgery had been undertaken. We contacted families by phone and updated any change in status from the time of last data collection. For those who had not developed scoliosis and their clinician had indicated no clinical signs of scoliosis present (category A), we administered a questionnaire to the family over the telephone at approximately three monthly intervals to identify any concerns about scoliosis raised by their clinician since the administration of our 2011 family questionnaire. If scoliosis had been diagnosed by the child's clinician, we collected data from spinal radiographs held at clinics and hospitals throughout Australia as well as those kept by parents at their home. Multiple pathways were therefore utilized to acquire Cobb angle data for each child across Australia. Telephone questionnaires were considered to be the most appropriate and efficient means of data collection for those children not undergoing regular specialist spine surveillance due to the large geographical distances between specialist care and the families location in Australia which has a land mass of 7.7 million square kilometres and mostly a single specialist spine deformity centre in the capital city of each state.

Experienced spinal surgeons or radiologists reviewed all radiographs and the magnitude of the scoliosis was measured using the method of Cobb.^{22,23} The pattern of the spinal curve (single [“c”] or double [“s”] curve), its location (thoracic, thoracolumbar, or lumbar), and the direction of the convexity (left or right) were documented. The location of the curve (thoracic, thoracolumbar, lumbar) was defined according to Scoliosis Research Society guidelines (http://www.srs.org/professionals/glossary/SRS_revised_glossary_of_terms.htm). If only the range of the curve was reported (e.g., T5-L2), then the apex was assumed to be at the midpoint. Cobb angles measured on radiographs taken while wearing a brace, in traction, in the supine position, or post surgery were excluded. Therefore, Cobb angle measurements included in the analyses were measured from x-rays taken in an erect position.

Ethics approvals for data access were obtained from the Princess Margaret Hospital for Children, Perth; Royal Perth Hospital, Perth; Women’s and Children’s Hospital, Adelaide; Royal Children’s Hospital, Melbourne; Monash Medical Centre, Melbourne; Sydney Children’s Hospitals Network, Sydney; Mater Health Services, Brisbane; and Royal Children’s Hospital, Brisbane.

Data analysis: For onset of scoliosis analysis, individuals were observed from date of birth and censored at age of diagnosis of scoliosis, age at death, or age at last contact date if alive. The Kaplan-Meier method was used to estimate the survival function and the median age of onset. The log-rank test was used to examine difference in time to onset across different mutation types. A multilevel mixed-effects linear regression model was used to explore the effects of age on the (square root) Cobb angle after adjusting for age at scoliosis onset. Square root transformation of Cobb angle was chosen because of the nonlinear pattern of Cobb angle change with age and this approach was used in a prior similar study.¹⁴ To investigate different trajectories by mutation type and ambulation status, age interaction terms were included in the model. A linear mixed model was chosen because it takes into account the within subject correlation of the dependent variable and can handle unbalanced data, assuming that the missingness was at random. The model incorporated random intercepts and slopes and was fitted using restricted maximum likelihood, an unstructured random-effects covariance, and an autoregressive (AR 1) residual correlation structure.

The probability of having a very severe scoliosis at age 16 years was evaluated using a logistic regression model that included the following predictors: Cobb angle at 10 years dichotomized into normal with no clinical signs of scoliosis/mild and moderate/severe group based on a minimum Cobb angle of 25°, and a categorical ambulation status indicator combining data from the variables learned to walk and ambulation status at 10 years ([1] learned to walk + independent walking, [2] learned to walk + assisted/not walking, [3] never learned to walk). The predictive performance of the logistic model was assessed using a receiver operating characteristics (ROC) curve. Data were analysed using Stata (version 13; StataCorp, College Station, TX, USA).

RESULTS

A population of 394 females with Rett syndrome whose parents/carers had provided information to the ARSD since 1993 and as at April 2015 was included in the study, among whom 73 had died. Nearly two-thirds of this population (n=261, 66.2%) were diagnosed with scoliosis. Four distinct groups of ambulation status were described: (1) always walked independently (n=131), (2) always walked with assistance (n=50), (3) always unable to walk (n=127), and (4) deteriorating from independent/assisted walking to unable to walk (n=55) (at any time during observation). The distributions of mutation type and ambulation status for the whole population and for the subset that developed scoliosis are shown in Table 1.

Based on 4286 person-years of observation in the whole study population (n=394), the estimated median age of onset of scoliosis was 11 years (95% confidence interval [CI] 10 years, 11 years 7 months) (Figure 1). The median onset age differed across mutation type ($P<0.001$). Individuals with p.Arg255* (4 years 6 months) and LD (7 years 10 months) mutations had the youngest median age of onset, while those with p.Arg294* (15 years 4 months) and p.Arg133Cys (12 years) mutations had relatively longer median time to onset (Table 1). For the subgroup that developed scoliosis, their median age of scoliosis onset was 8 years 9 months (95% CI 8 years, 9 years 5 months).

Cobb angle measures were available for 196 (75.1% of the 261 with scoliosis) individuals. The majority had a right sided curve (59.2%, n=116) and the curves were mostly thoracic (44.9%, n=88) or thoracolumbar (26.5%, n=52).

Approximately two-thirds (65.3%, n=128) had at least three Cobb angle time point measures taken from erect radiographs with 666 Cobb angle measures in total available for analysis. Nearly half (46.9%, n=60) were “always wheelchair dependent” and 21.1% (n=27) were “always able to walk independently.” The distribution of mutation types and ambulation status for this subgroup is shown in Table 1 and the timing of deteriorating ambulation status in Table 2.

Each year increase in age was associated with a 0.438 unit increase in the square root of the Cobb angle (95% CI 0.374, 0.503; $P < 0.001$) in the 128 individuals for whom we had at least three Cobb angle measures. Cobb angle values for each mutation group are shown as a scatterplot (Figure 2A) and fitted as trajectories (Figure 2B). Compared to the LD group, those with a CT, ET, p.Arg133Cys, p.Arg168*, p.Arg255*, p.Arg270*, and p.Arg306Cys mutation had smaller annual increases in Cobb angle after controlling for walking status and age of scoliosis onset (Table 3). Cobb angle values for each ambulation group are shown as a scatterplot (Figure 3A) and fitted as trajectories (Figure 3B). Compared to those who walked independently, those who never learned to walk and those whose walking deteriorated had a more rapid annual increase in Cobb angle. The rate of change of Cobb angle was not significantly different between those who walked independently and those who walked with assistance (Table 3). Figures 2 and 3 illustrate the effects of mutation type and ambulation status on the trajectory.

Using the binary Cobb angle and ambulation indicators at 10 years (available for 106 individuals) as predictors, a Logistic model on prediction of very severe scoliosis (Cobb angle $\geq 60^\circ$) by 16 years was developed. The area under the ROC curve of the model was 0.888 (Figure 4). Using a cut-off point of 0.5, the sensitivity and specificity of the model were 74.6% and 82.4%, respectively, with high positive (82.0%) and negative (75.0%) predictive values. Accordingly, it is predicted that an individual with normal/mild scoliosis (Cobb angle $< 25^\circ$) and independent walking at 10 years has a 12.9% (95% CI 3.7%, 22.1%) risk of developing very severe scoliosis by 16 years, compared to 98.9% (95% CI 96.7%, 100%) risk if moderate/severe Cobb angle ($> 25^\circ$) and unable to walk were present at 10 years.

DISCUSSION

Three quarters of the Australian population with Rett syndrome have developed scoliosis, a serious comorbidity that can be associated with pain, deterioration of motor skills and a restrictive respiratory function.²⁴ We were previously the first to investigate the age of onset of scoliosis with a population-based sample of 231 girls and women published in 2006.⁸ We have continued to maintain the ARSD ascertaining new cases nationally²¹ and therefore the population of the current study is considerably larger than our earlier work. In nearly 400 girls and women with Rett syndrome, we confirm that scoliosis occurs in the majority, with 75% developing scoliosis by the age of 15 years rather than by 13 years as previously estimated.⁸ The age of onset of scoliosis is strongly influenced by genotype, with mutations associated with milder disease^{16,25} associated with later onset of scoliosis. Genetic testing has now been available for 15 years and our findings are consistent with greater recognition that a milder phenotype is associated with mutations such as the p.Arg294*, p.Arg133Cys, p.Arg306Cys and CT mutations.^{16,26}

The magnitude of scoliosis in our Rett syndrome population was found to generally increase with age as has been observed with other populations with a neuromuscular scoliosis.^{14,15} In Rett syndrome, the type of genetic mutation was generally associated with scoliosis progression. For example mutations associated with a more severe clinical phenotype such as LD or the p.Arg270* mutation^{16,25} were associated with greater progression of scoliosis and extra vigilance in monitoring of these children would seem indicated. In contrast, mutations associated with a milder phenotype^{16,25} were associated with less progression and may therefore require less frequent observation and radiographic surveillance. Those with the p.Arg306Cys mutation were unique in demonstrating very little progression of their scoliosis. Interestingly, those with the p.Arg294* mutation were generally protected from the development of any scoliosis but for those who did develop scoliosis, progression of the curve was often fulminant and would suggest these children warrant extra vigilance in the monitoring of their scoliosis.

The trajectory of ambulation status was particularly strongly associated with the trajectory of scoliosis. Those who maintained the ability to walk independently or the ability to walk with assistance during childhood did not exhibit the marked progression of scoliosis observed in those who never learned to walk or in those whose walking skills

deteriorated. Girls unable to walk would be likely to have more severe neurological impairment affecting muscle tone, which may result in the greater risk of scoliosis development. Those whose ability to walk deteriorated were at similar risk of marked scoliosis progression, consistent with observations in cerebral palsy where scoliosis deteriorated rapidly if motor skills deteriorated.¹⁴ Deterioration in walking ability usually preceded marked progression of scoliosis and this temporal relationship has led to some suggestion that walking may have a protective role for spinal health. Physical activity is associated with health benefits for those with disability²⁷ and walking is likely similarly valuable for those with Rett syndrome. However, a cause and effect relationship cannot be determined because the possibility also exists that the loss of walking was associated with a more severe phenotype.

The likelihood of developing a very severe scoliosis at 16 years based on clinical data available at 10 years of age was also modeled. Data from when the children were 10 years old were used to predict outcomes at 16 years of age, because this time frame is consistent with the time frame during which spinal fusion surgery has been typically performed in Rett syndrome.²⁸ The model showed good predictive performance (sensitivity and specificity) in quantifying this risk. For example, those with capacity to walk independently at 10 years and with no or a mild scoliosis were unlikely to develop a very severe scoliosis. This informs predicted outcomes and guides the frequency of clinical and radiographic surveillance likely to be required in the years to follow. Conversely, those unable to walk and with a moderate to severe scoliosis at 10 years were at particular risk of progression and potentially more likely to need spinal fusion and therefore more frequent clinical and radiographic surveillance.

A scoliosis convex to the right was more frequently observed, consistent with observations by Bengt Hagberg¹¹ of a series of 24 females with Rett syndrome in whom the convexity of scoliosis, foot deformities and limb atrophy were more commonly observed on the right side.¹¹

The foundation of our dataset was the population-based and longitudinal ARSD enriched with substantial clinical data from all the major spine deformity centres in Australia. We acknowledge that the timing of reimaging was not standardized. Radiographs were undertaken at clinically determined by the individual spinal orthopaedic surgeons at

their discretion. The radiographs were taken in different radiology departments and Cobb angles were measured by multiple clinicians as part of standard practice. We acknowledge the potential for variation in the quality of the radiographs and for inter-rater error to effect the measurement. The literature suggests an inter-rater error of approximately 6° to 7° with manual measurement²⁹ and good inter-rater reliability using computerised systems,³⁰ and both systems were used in the current study. The error in our study is not known. However, each clinician was a specialist in spinal orthopaedics and these data have informed their clinical decision making. The current study is therefore pragmatic and highly relevant to clinical care. We also acknowledge that we had fewer than three Cobb angles on a greater proportion of those who walked than did not, and that we may have underestimated the benefit of walking on the progression of scoliosis. This is an understandable outcome in a natural history study given that those who walked tended to have smaller Cobb angles and despite regular spine reviews with specialist spine orthopaedic surgeons, they had fewer radiographs ordered with medical records entries instructing “for clinical review only, no radiograph required.”

Our data describing the onset and trajectories of scoliosis in Rett syndrome provide a framework comprising population data that can assist in the understanding of risk in relation to individual clinical scenarios. A progressive and severe scoliosis is of immediate clinical concern and guides the decision to proceed to surgical correction.³¹ Novel data from this study on the progression of scoliosis in Rett syndrome and influencing factors will inform decision making regarding the likelihood of need for surgical correction and assist the clinician to facilitate optimum monitoring practices including the frequency of surveillance radiographs in this population.

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		Whole Population in ARSD (N = 394)*		Subgroup Who Developed Scoliosis (N = 261) [†]	Subgroup Who Developed Scoliosis and With At Least Three Cobb Angle Measures (N = 128)
		N (%)	Median age of scoliosis diagnosis (95% CI)	N (%)	N (%)
Mutation type	C-terminal	27 (6.9)	11 (10,14.5)	20 (7.7)	7 (5.5)
	ET	21 (5.3)	8.5 (7,11.4)	18 (6.9)	10 (7.8)
	LD	23 (5.8)	7.8 (4.8,11.6)	20 (7.7)	13 (10.2)
	p.Arg106Trp	14 (3.6)	10 (5.4,17)	9 (3.5)	4 (3.1)
	p.Arg133Cys	23 (5.8)	12 (9.5,14.9)	15 (5.8)	6 (4.7)
	p.Arg168 [‡]	32 (8.1)	8 (5.9,11.6)	22 (8.4)	15 (11.7)
	p.Arg255 [‡]	18 (4.6)	4.5 (3,9.6)	16 (6.1)	10 (7.8)
	p.Arg270 [‡]	26 (6.6)	9.5 (7,11)	18 (6.9)	12 (9.4)
	p.Arg294 [‡]	24 (6.1)	15.3 (12,-)	12 (4.6)	3 (2.3)
	p.Arg306Cys	18 (4.6)	11 (8,14.4)	13 (5.0)	3 (2.3)
	p.Thr158Met	31 (7.9)	8.5 (6,12)	20 (7.7)	12 (9.4)
	Other	37 (9.4)	11 (7.4,14)	24 (9.2)	15 (11.7)
	Negative	61 (15.5)	13.3 (11,23.8)	34 (13.0)	15 (11.7)
Ambulation trajectory	Independent	131 (33.3)	15.0 (14,-)	64 (24.5)	27 (21.1)
	Assisted	50 (12.7)	10.4 (9.0,11.6)	44 (16.9)	19 (14.8)
	Deteriorating	55 (14.0)	9.1 (8,10.4)	42 (16.1)	20 (15.6)
	Unable to walk	127 (32.2)	8 (6,8.8)	106 (40.6)	60 (46.9)
<p>*Mutation type available for 355 (90.1%), ambulatory trajectory available for 363 (92.1%).</p> <p>[†]Mutation status available for 241 (92.3%), ambulatory trajectory available for 256 (98.1%).</p> <p>[‡]Statistical significance.</p> <p>ARSD indicates Australian Rett Syndrome Database; CI, confidence interval; ET, early truncating; LD, large deletion.</p>					

Table 1: Mutation type and ambulation status of the population in the Australian Rett Syndrome Database, Those who developed a scoliosis and those for whom at least 3 Cobb angles were available to define the trajectory of their scoliosis.

Table 2. Median (IQR) age of deterioration in mobility status

Change in mobility status	n	Median (interquartile range) age in years
Assisted walking to wheelchair bound	16	9 (7-12)
Independent to assisted walking	3	6 (5-13)
Independent walking to wheelchair bound	1	7

Table 3. Description of relative differences in change in Cobb angle compared with the reference groups of the LD mutation and independent walking (n=128)

		Change in Annual Increase Compared to Reference Group	
		Coefficient (95% CI)	P
Mutation type*	LD	Ref	—
	C-terminal	−0.024 (−0.404,0.355)	0.899
	ET	−0.131 (−0.444,0.181)	0.410
	p.Arg106Trp	0.020 (−0.461,0.501)	0.936
	p.Arg133Cys	−0.162 (−0.529,0.206)	0.389
	p.Arg168 [†]	−0.050 (−0.328,0.228)	0.723
	p.Arg255 [†]	−0.132 (−0.432,0.168)	0.389
	p.Arg270 [†]	−0.133 (−0.421,0.155)	0.366
	p.Arg294 [†]	0.364 (−0.109,0.837)	0.131
	p.Arg306Cys	−0.415 (−0.852,0.023)	0.063
	p.Thr158Met	0.012 (−0.291,0.314)	0.941
	Other	−0.068 (−0.354,0.218)	0.642
	Negative	−0.037 (−0.322,0.247)	0.798
Ambulation trajectory [‡]	Independent	Ref	—
	Assisted	−0.016 (−0.212,0.180)	0.871
	Deteriorating	0.246 (0.045,0.446)	0.016
	Unable to walk	0.176 (0.014,0.337)	0.033

*Adjusted for age at scoliosis onset and ambulatory trajectory.
[†]Adjusted for age at scoliosis onset and mutation status.
[‡]Statistical significance.
CI indicates confidence interval; Ref, reference group; ET, early truncating; LD, large deletion.

Figures

Figure 1: Kaplan-Meier function of time to onset of scoliosis in girls and women with Rett syndrome (n=394)

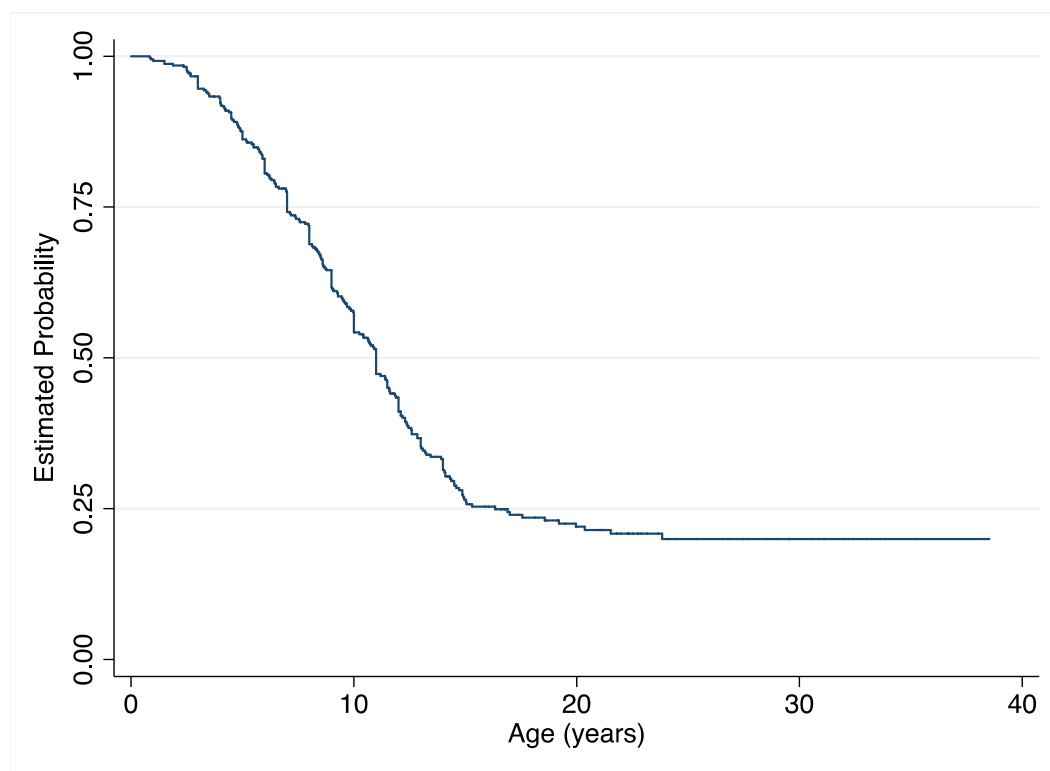


Figure 2. A. Scatterplot of individual data and B. fitted Cobb angle trajectories by mutation type (n=128)

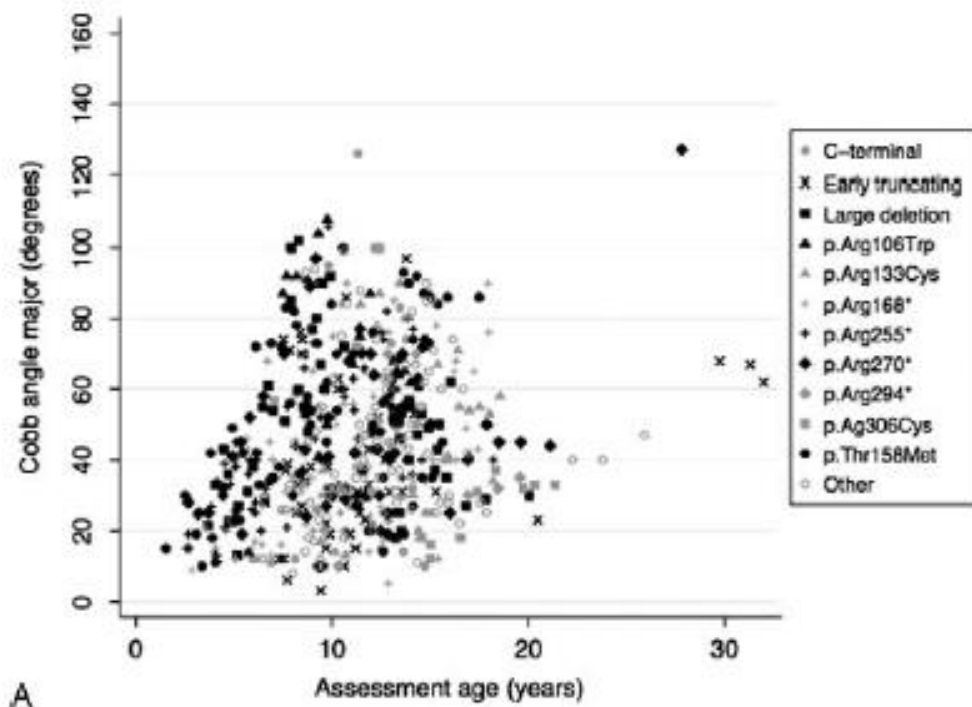
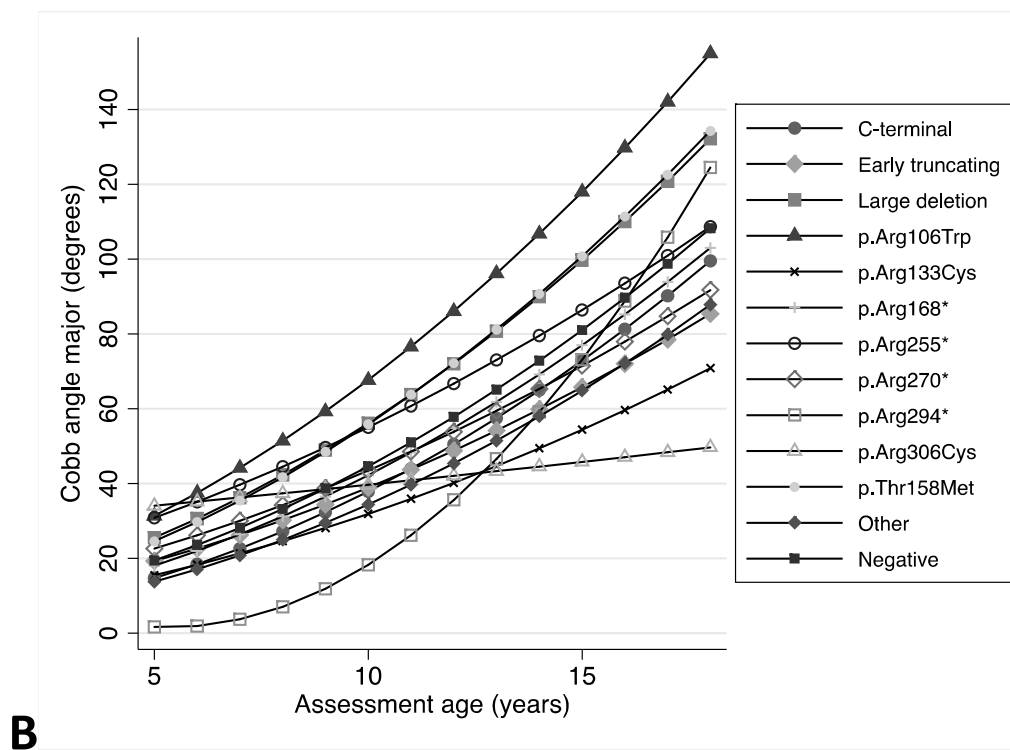
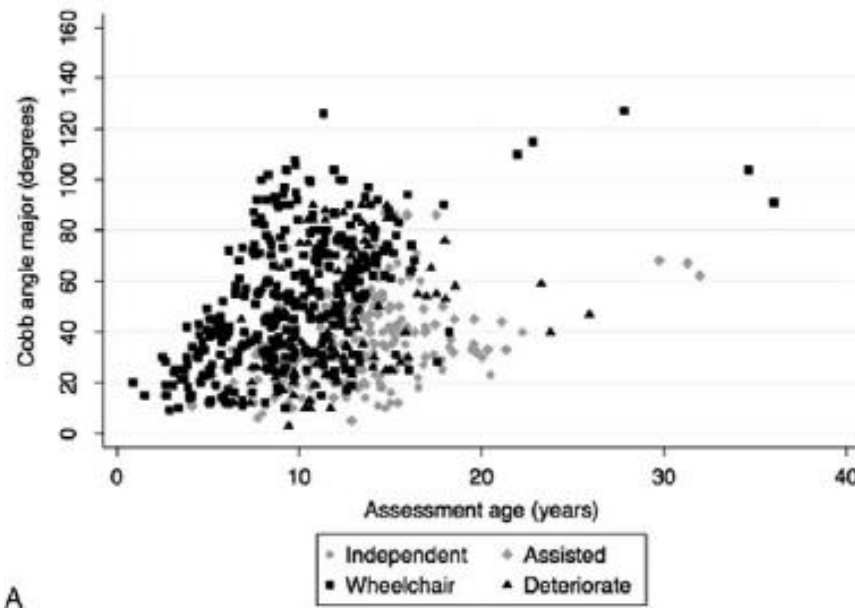
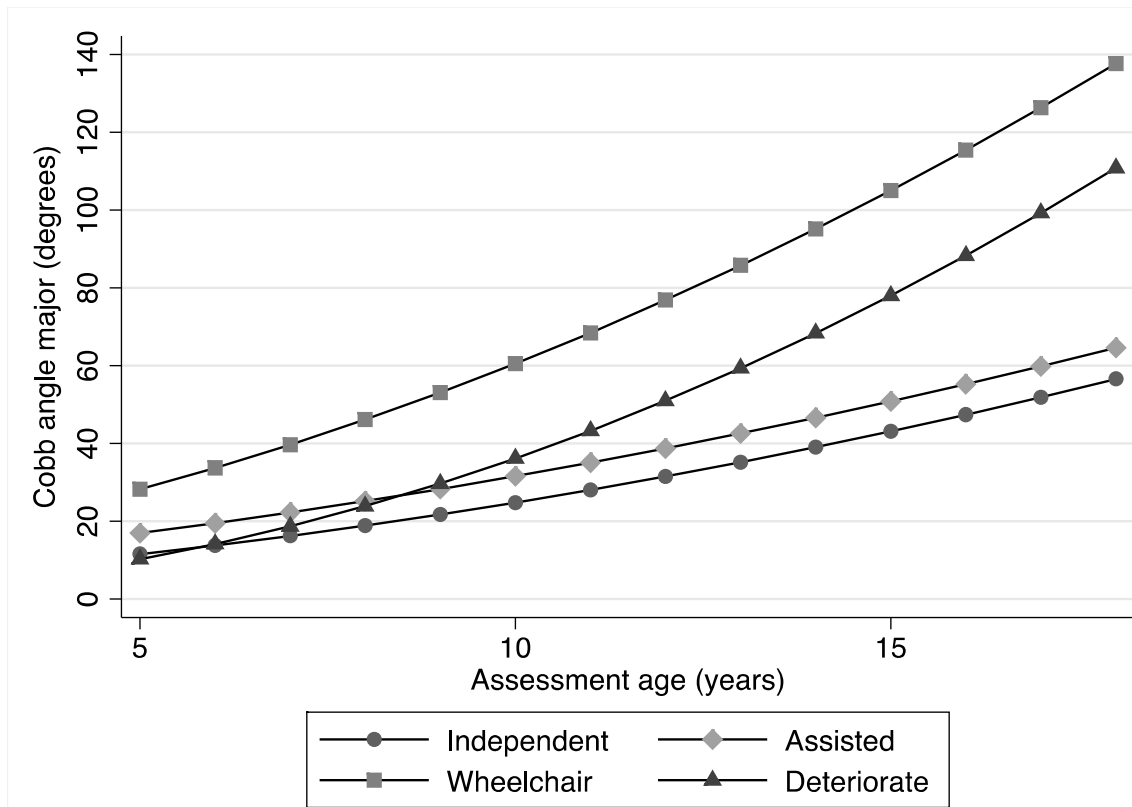
**A****B**

Figure 3. A. Scatterplot of individual data and B. fitted Cobb angle trajectories by ambulation status (n=128)



A



B

Figure 4. The ROC curve of a logistic regression model to predict the likelihood of very severe scoliosis (Cobb angle $> 60^\circ$) by 16 years in Rett Syndrome ($n = 106$). ROC indicates receiver operating characteristics.

