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# Aspects of Speech-Language Abilities are Influenced by *MECP2* Mutation Type in Girls With Rett Syndrome

Anna Urbanowicz,<sup>1,2</sup> Jenny Downs,<sup>1,3</sup> Sonya Girdler,<sup>4</sup> Natalie Ciccone,<sup>5</sup> and Helen Leonard<sup>1\*</sup>

<sup>1</sup>Telethon Kids Institute, The University of Western Australia, Australia

<sup>2</sup>School of Exercise and Health Sciences, Edith Cowan University, Perth WA, Australia

<sup>3</sup>School of Physiotherapy and Exercise Science, Curtin University, Perth WA, Australia

<sup>4</sup>School of Occupational Therapy and Social Work, Centre for Research into Disability and Society, Curtin University, Perth WA, Australia

<sup>5</sup>School of Psychology and Social Science, Edith Cowan University, Perth WA, Australia

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This study investigates relationships between methyl-CpG-binding protein 2 gene (*MECP2*) mutation type and speech-language abilities in girls with Rett syndrome. Cross-sectional data on 766 girls, aged 15 years and under, with genetically confirmed Rett syndrome was obtained from the Australian Rett Syndrome Database (ARSD) ( $n = 244$ ) and the International Rett Syndrome Phenotype Database (InterRett) ( $n = 522$ ). Relationships between *MECP2* mutation type and age of regression in speech-language abilities, and the level of speech-language abilities before and after this regression were investigated. The females had a median age of 4.95 years in the ARSD and 5.25 years in InterRett. The majority (89%, 685/766) acquired speech-language abilities in the form of babble or words at some point in time. Of those who acquired babble or words, 85% (581/685) experienced a regression in these abilities. Those with a p.Arg133Cys mutation were the most likely to use one or more words, prior to (RRR = 3.45; 95% CI 1.15–10.41) and after (RRR = 5.99; 95% CI 2.00–17.92), speech-language regression. Girls with Rett syndrome vary in their use of speech and language, and in their experience of speech-language regression and these variations are partly explained by genotype.

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**Key words:** Rett syndrome; *MECP2*; speech; language; regression; genotype–phenotype correlation

## INTRODUCTION

Language is one of the most commonly used forms of communication for people of all ages but speech-language abilities are almost always severely impaired in the neurodevelopmental disorder Rett syndrome. Rett syndrome is primarily caused by mutations in the X-linked methyl-CpG-binding protein 2 gene (*MECP2*) [Amir et al., 1999]. A period of developmental regression, during which spoken language and hand skills are partially or completely lost, is one of the essential criteria required for a diagnosis of typical Rett

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syndrome. Other essential criteria are the development of hand stereotypies and impaired mobility [Neul et al., 2010]. Comorbidities including seizures [Bao et al., 2013], scoliosis [Ager et al., 2006] and breathing disturbances [Ramirez et al., 2013] may also develop over time. There is considerable variability in the severity of these clinical features among affected girls and women [Bebbington et al., 2008], and as such there are also atypical presentations of Rett syndrome that do not always conform to the outlined typical criteria [Neul et al., 2010].

The foundations of later speech-language abilities are established in the first year of life [Owens, 2012]. Early development of speech and language involves the production of cries and pleasure sounds. Later, between four and nine months of age, typically developing children start to babble by producing combinations of consonant-vowel sounds [Sharma and Cockerill, 2014]. They also start to understand spoken language prior to the development of more complex expressive language abilities, such as vocalisations with

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\*Correspondence to:

Helen Leonard, Telethon Kids Institute, The University of Western Australia, PO Box 855, West Perth, Western Australia, 6872.

E-mail: helen.leonard@telethonkids.org.au

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meaning and words [Owens, 2012; Sharma and Cockerill, 2014]. Vocalizations with meaning, such as “da” for dad, usually develop between the ages of 9 and 12 months and words commonly begin to emerge between 12 and 15 months [Sharma and Cockerill, 2014]. Many girls and women with Rett syndrome learn to say words at some point in time [Uchino et al., 2001; Bartolotta et al., 2011], although the development of speech-language abilities may be delayed and atypical [Tams-Little and Holdgrafer, 1996; Marschik et al., 2012]. The majority of girls and women experience a regression in speech and language abilities between 12 and 24 months of age [Uchino et al., 2001; Bartolotta et al., 2011]. Following the regression period, only between 6% (20/331) [Kerr et al., 2006] and 18% (29/158) [Renieri et al., 2009] of girls and women have been reported to say words. Some have characterized this group as the preserved speech variant of Rett syndrome [Zappella et al., 1998]. Little is known about other speech-language abilities, such as the ability to babble and vocalize [Marschik et al., 2013]. These studies are the largest to date to specifically describe the use of and regression of speech-language abilities in Rett syndrome, but they have some methodological limitations in terms of the validation of diagnosis [Bartolotta et al., 2011], criteria used to describe language abilities [Uchino et al., 2001; Kerr et al., 2006; Renieri et al., 2009] and population representativeness [Uchino et al., 2001; Renieri et al., 2009; Bartolotta et al., 2011].

The successful development of speech and language is reliant on a number of genetic and environmental factors [Sharma and Cockerill, 2014]. The *MECP2* gene is responsible for the production of the MeCP2 protein, which is important in the development and maintenance of the brain and nervous system [Cohen et al., 2011]. Relationships between *MECP2* mutation type and general clinical severity, as well as specific features, have been identified in Rett syndrome [Bebbington et al., 2008; Neul et al., 2008; Cuddapah et al., 2014]. It is not known if MeCP2 plays a specific role in the development of speech-language abilities but some relationships between *MECP2* mutation type and speech-language abilities have been identified in Rett syndrome. For example, in an international study ( $n = 276$ ), girls and women with a p.Arg133Cys mutation were more likely to use single words and phrases, and those with a p.Arg270X or a p.Arg255X mutation less likely to acquire the ability to speak, compared to the overall sample [Bebbington et al., 2008]. Genotype also appears to influence the age at which girls experience developmental regression, with those with a p.Arg133Cys, p.Arg294X [Bebbington et al., 2008] or C-terminal deletion [Fehr et al., 2011] reported to regress later. However, it is still not known how genotype may influence other speech-language abilities such as babbling, and the timing of speech-language regression.

There remains the need to describe a range of speech-language abilities in a sample of girls with Rett syndrome large enough to fully investigate the effect of genotype, as the complete picture is unclear from the literature [Uchino et al., 2001; Kerr et al., 2006; Bebbington et al., 2008; Neul et al., 2008; Bartolotta et al., 2011; Cuddapah et al., 2014]. We therefore conducted a study using a large sample of girls with Rett syndrome sourced from two databases, the population-based Australian Rett Syndrome Database (ARSD) [Downs et al., 2008] and the International Rett Syndrome Phenotype Database (InterRett) [Moore et al., 2005;

Louise et al., 2009], to describe a range of speech-language abilities and to investigate relationships with genotype.

## MATERIALS AND METHODS

### Data Management

Data from the ARSD and InterRett were used in this study. The ARSD was established in 1993 and continues to collect longitudinal data on Australian girls and women with Rett syndrome born since 1976 [Downs et al., 2008]. InterRett was established in 2002 and collects cross-sectional data on girls and women with Rett syndrome from 54 countries around the world [Moore et al., 2005; Louise et al., 2009]. Upon enrollment into either database, questionnaires are completed by caregivers and/or clinicians who provide data on the early development, regression period and current functioning of the girl or woman with Rett syndrome. Girls with a pathogenic *MECP2* mutation, who were 15 years or younger at the time of questionnaire completion, and whose parents had provided data on regression in speech-language abilities, and the level of speech-language abilities before and after this regression, were eligible for this study. The age limit for eligible girls was restricted to 15 years and younger to minimise potential caregiver recall error [Majnemer and Rosenblatt, 1994; Russell et al., 2014] but still capture those girls that may experience a late regression in speech-language abilities [Hagberg and Skjedal, 1994].

In terms of speech-language abilities, the questionnaire asked parents about their daughter's best level of ability before and after speech-language regression with options being; no speech or language, babble, vocalizations with meaning, single words, two word combinations, three word combinations and, four or more word combinations. Using this information the level of speech-language abilities was coded for analysis as one of the following mutually exclusive categories; no speech or language, use of babble, or use of words. There was only a small number of girls able to combine words in our sample; 3.81% (22/577) of girls after experiencing an initial regression in speech-language abilities and 8.11% (15/185) of girls who did not experience speech-language regression. Therefore we combined girls able to use word combinations with those able to use vocalizations with meaning or single words in the “use of words” category for analyses. Only those who acquired some form of speech or language could be coded as experiencing a regression in speech-language abilities. The type of *MECP2* mutations was categorized as one of the following: early truncation, large deletion, C-terminal deletion, p.Arg106Trp, p.Arg133Cys, p.Arg168X, p.Arg255X, p.Arg270X, p.Arg294X, p.Arg306Cys, p.Thr158Met, or a group of other miscellaneous mutations.

### Data Analysis

Univariate linear regression was used to analyze the relationship between genotype and the age of speech-language regression. Logistic regression was used to determine the relationship between genotype and likelihood of reporting a regression in speech-language abilities and multinomial logistic regression was used to examine the relationships between genotype and the level of speech-language abilities. STATA software was used for statistical analyses [StataCorp, 2011]. This study was approved by the Princess

Margaret Hospital for Children and the Edith Cowan University Human Research Ethics Committees.

## RESULTS

At the time of analysis the ARSD contained data on 244 eligible cases with a median age of 4.95 years (range 1.45–15.0 years) at ascertainment and InterRett contained data on 522 eligible cases with a median age of 5.25 years (range 1.16–14.95 years) at ascertainment. The most common point mutations were p.Thr158Met (11.75%, 90/766), p.Arg168X (10.18%, 78/766) and C-terminal deletions (9.65%, 74/766). The majority of girls, 89.43% (685/766), were reported to acquire some speech-language abilities in the form of babble or words at some point in time. Of the girls with some acquired babble or words, 84.82% (581/685) were reported to have experienced a regression in these abilities (Fig. 1). The median age at this regression was 18 months (range 0.33–7.50 years) ( $n = 495$ ) and girls with a C-terminal deletion (RRR = 5.80; 95% CI 0.92–10.65) or a p.Arg294X mutation (RRR = 5.25; 95% CI 0.19–10.31) experienced a regression in speech-language abilities approximately five months after those with a large deletion (Fig. 2). We did not find statistically significant relationships between *MECP2* mutation type and the likelihood of reporting a regression in speech-language abilities (Table I).

The highest level of speech-language abilities acquired prior to experiencing a regression in speech or language was words for 77.43% (422/545) and babble for 22.57% (123/545). In comparison to girls with a large deletion, girls with a p.Arg133Cys mutation (RRR = 3.45; 95% CI 1.15–10.41) were the most likely to be able to say words prior to speech regression (Table II). After speech-language regression 21.49% (124/577) used words, 38.47% (222/577) were babbling and 40.03% (231/577) did not use babble or words. Of those girls able to use words after experiencing a regression in speech-language abilities, 17.74% (22/124) used word combinations, 13 combined two words, seven combined three words and two combined four or more words.

Those with a p.Arg133Cys (RRR = 5.99; 95% CI 2.00–17.92) remained the most likely to have the ability to say words after speech-language regression. Girls with a p.Arg168X mutation (RRR = 3.43; 95% CI 1.10–10.70) or a p.Arg306Cys mutation (RRR = 3.70; 95% CI 1.21–11.31) were also more likely to have the ability to say words after experiencing a regression in speech-language abilities in comparison to those with a large deletion. Girls with a p.Thr158Met mutation (RRR = 4.76; 95% CI 1.87–12.10) or a p.Arg294X mutation (RRR = 4.62; 95% CI 1.71–12.52) were the most likely to be babbling after speech-language regression (Table II).

For those who did not experience a regression in speech-language abilities ( $n = 185$ ) the highest level of speech or language ever acquired was babble for 31.35% (58/185) and words for 24.87% (46/185), while 43.78% (81/185) never developed any speech or language. Of those girls able to use one or more words, 30.61% (15/46) used word combinations, one combined two words, six combined three words and eight combined four or more words. All mutations types were represented in the group of girls without a speech regression. The p.Arg255X (61.11%, 11/18) and p.Thr158Met (60.87%, 14/23) mutation groups had the highest

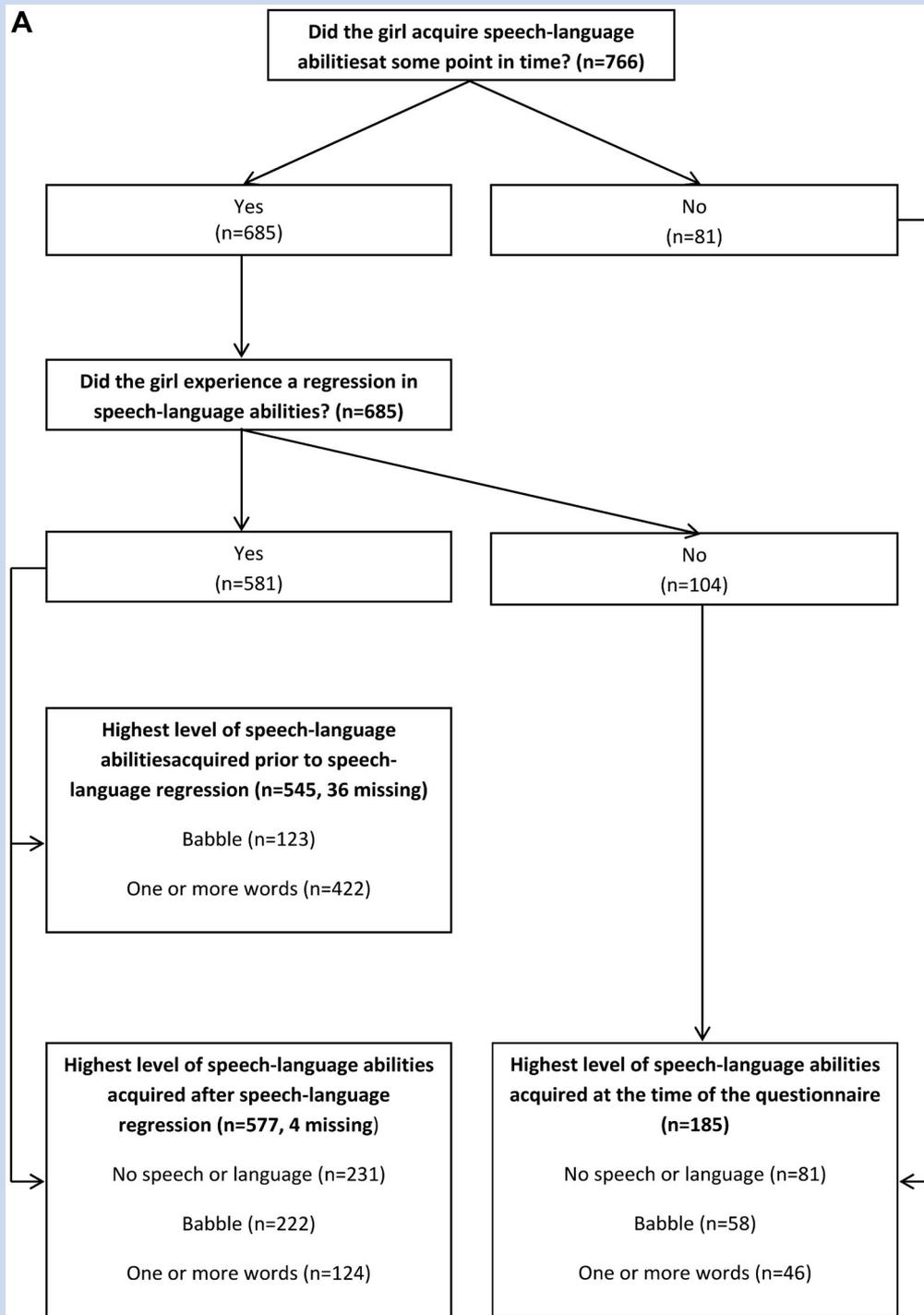
proportion of girls without any speech or language, and the C-terminal deletion (57.89%, 11/19) and p.Arg133Cys (50.00%, 4/8) mutation groups had the highest proportion of girls with the ability to use words (Table III).

## DISCUSSION

This study investigated speech-language abilities in one of the largest samples of girls with Rett syndrome to date. Accordingly, we have been able to explore variations in speech-language abilities among the girls and investigate relationships with genotype that were not previously possible. We found that the majority of the girls acquired babble or words at some point in time and that most, but not all, experienced a regression in these abilities. For those who did experience a speech-language regression, over two thirds used words before this regression but less than one fifth said words afterwards. The variation observed in speech-language abilities and age of speech-language regression was partly explained by genotype. Consistent with previous literature, individuals with mutations associated with milder presentations were more likely to use words before and after speech-language regression, and regress later than those with mutations associated with more severe presentations.

A major strength of this study is the combined use of a population-based and an international data source providing information on over 700 girls with a diagnosis of Rett syndrome, confirmed with the presence of a pathogenic *MECP2* mutation. International databases such as InterRett [Moore et al., 2005; Louise et al., 2009] provide the capacity to investigate relationships between genotype and features of Rett syndrome as these analyses require a large sample size often not available otherwise [Leonard et al., 2013]. This study has therefore been able to provide greater insights into the relationships between genotype and speech-language abilities than previously documented [Bebbington et al., 2008; Neul et al., 2008; Cuddapah et al., 2014]. For example, it was already documented that individuals with a p.Arg133Cys mutation generally experience a milder presentation of Rett syndrome [Leonard et al., 2003] but we now also know that they experience speech-language regression later than those with other mutations. With the use of a large sample we have also been able to expand our knowledge of girls who are not well represented in the literature including those with less common *MECP2* mutations and those who did not experience a regression in speech-language abilities. For example, previous investigations have been limited in their capacity to provide insights into the relationships between the less common p.Arg106Trp mutation and clinical features of Rett syndrome due to including only nine [Neul et al., 2008] or 18 females with this mutation. [Bebbington et al., 2008].

Studies utilizing retrospective parent report have some inherent methodological limitations such as recall error [Ozonoff et al., 2011; Zwaigenbaum et al., 2013]. However parent report questionnaires are useful in the study of large sample sizes with participants from varying geographical locations where it may not be feasible to use more direct methods for data collection such as video analysis [Leonard et al., 2013]. Some of our data was retrospective in that we asked parents about speech-language regression and their daughter's speech-language abilities prior to this regression, which usually occurs in the first few years of life [Neul et al., 2010; Lee et al., 2013].



**FIG. 1.** Flow chart describing the speech-language abilities and regression in speech-language abilities in our sample (n = 766).

We minimized the potential for recall error by limiting the age of our sample to girls aged 15 years or younger at the time of questionnaire completion. We also asked parents about their daughter's speech-language abilities at the time of questionnaire completion and there is some evidence to support agreement between parent report data on current communication abilities and data reported by profes-

sionals [Bartolotta et al., 2011] or collected from direct assessment [Eadie et al., 2010]. Furthermore in our study parents did not have to complete every question in the questionnaire if they were unsure of the answer, as a result we have some missing data but the data we have collected may be more reliable. Another limitation is that our categories of speech-language abilities cannot distinguish variations

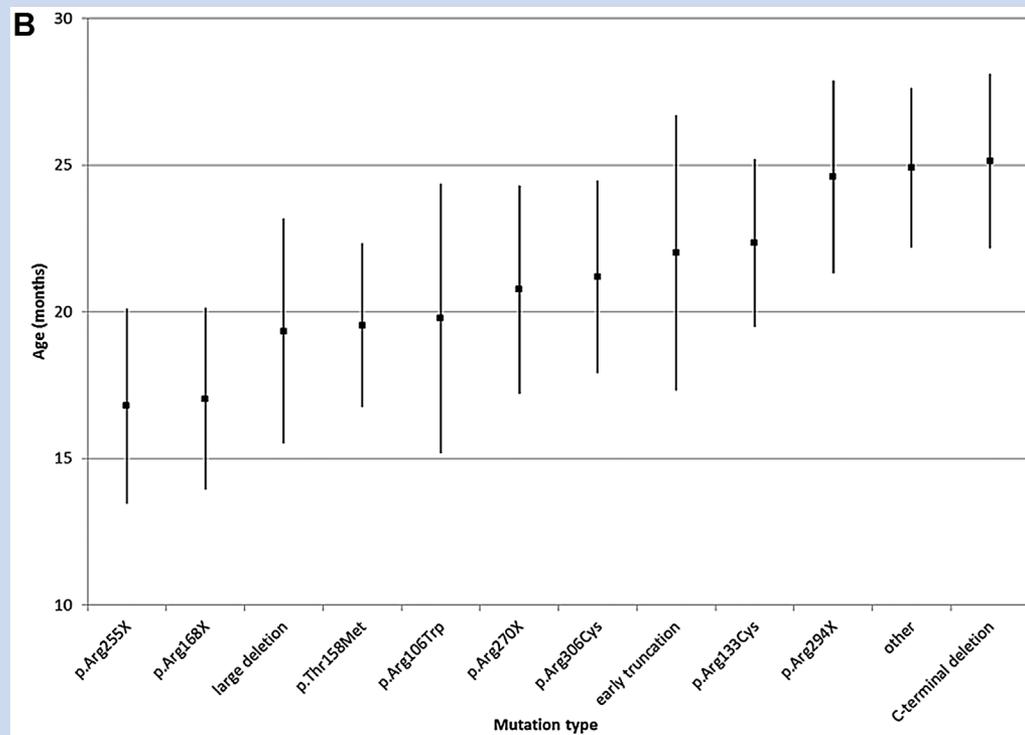


FIG. 2. Adjusted mean age of regression of speech-language abilities (months) by type of mutation with 95% confidence intervals (n = 495).

in ability within each category. For example those who have just begun to babble and those who may have more complex babbling would be categorized similarly. Factors that might account for variability in speech-language abilities within each mutation category, including epigenetic factors such as X-inactivation status

[Archer et al., 2006] and environmental factors such as interventions targeting communication abilities [Bartolotta and Remshifski, 2013; Urbanowicz et al., 2014], were not able to be investigated in this study. Furthermore in a small number of cases the questionnaire may have been completed prior to regression in speech-language abilities and thus we could have underestimated the proportion with a regression of speech-language abilities.

Generally, our results confirm previous investigations, each with their own strengths and limitations, which reported the ability to use words varied in Rett syndrome [Uchino et al., 2001; Kerr et al., 2006; Bartolotta et al., 2011; Marschik et al., 2013]. In our study, 77% of girls said words prior to a regression in speech-language abilities. This is similar to the 70% reported to use meaningful words at some point in time from a survey of 141 parents, teachers and speech-language pathologists [Bartolotta et al., 2011]. Our results may be more accurate as the diagnosis of Rett syndrome was not confirmed in the Bartolotta et al. [2011] survey and since their survey was completed anonymously, there could be duplicate entries on the same individual by different respondents. After language regression, 21% of our sample used words, similar to the proportion of 18% reported in a study using data from the British Isles Survey for Rett on girls and women aged over 10 years, with a pathogenic *MECP2* mutation (n = 331) [Kerr et al., 2006]. From our study we can estimate that for girls who experience a regression in speech-language abilities, approximately three quarters will have the ability to say words prior to regression, but less than one fifth will continue to have this ability.

TABLE I. Likelihood of Experiencing a Regression in Speech-Language Abilities by Type of Mutation (n = 766)

Mutation type (n)	Regression in speech	
	RRR (95% CI)	P-value
large deletion (53)	—	—
p.Arg106Trp (35)	0.94 (0.35–2.51)	0.90
p.Arg133Cys (63)	2.23 (0.85–5.90)	0.10
p.Arg168X (78)	0.65 (0.30–1.42)	0.28
p.Arg255X (67)	0.88 (0.39–2.02)	0.77
p.Arg270X (57)	0.83 (0.35–1.95)	0.67
p.Arg294X (61)	1.33 (0.55–3.23)	0.53
p.Arg306Cys (54)	2.18 (0.79–6.00)	0.13
p.Thr158Met (90)	0.95 (0.43–2.07)	0.89
C-terminal deletion (74)	0.94 (0.42–2.12)	0.88
early truncation (45)	0.49 (0.20–1.16)	0.10
other (89)	1.48 (0.65–3.39)	0.35

**TABLE II. Likelihood of Speech-Language Abilities Before and After Experiencing a Speech-Language Regression by Type of MECP2 Mutation**

Pre-regression level of speech-language abilities (n = 545)					
Mutation type (n)	Babble		Words		
	Base outcome	RRR (95% CI)	P-value	RRR (95% CI)	P-value
large deletion (37)		—	—	—	—
p.Arg106Trp (24)		0.85 (0.28–2.55)			0.77
p.Arg133Cys (55)		3.45 (1.15–10.41)			0.03
p.Arg168X (48)		1.14 (0.44–2.94)			0.79
p.Arg255X (46)		0.87 (0.34–2.23)			0.78
p.Arg270X (39)		0.75 (0.29–1.98)			0.57
p.Arg294X (45)		3.38 (1.05–10.87)			0.04
p.Arg306Cys (44)		2.24 (0.76–6.53)			0.14
p.Thr158Met (63)		1.48 (0.59–3.72)			0.40
C-terminal deletion (53)		2.07 (0.76–5.65)			0.16
early truncation (24)		1.03 (0.33–3.17)			0.96
other (67)		1.60 (0.64–4.01)			0.31
Post-regression level of speech-language abilities (n = 577)					
Mutation type (n)	No speech or language	Babble		Words	
	Base outcome	RRR (95% CI)	P-value	RRR (95% CI)	P-value
large deletion (40)		—	—	—	—
p.Arg106Trp (25)		4.32 (1.39–13.40)	0.01	0.92 (0.16–5.45)	0.93
p.Arg133Cys (55)		2.78 (0.99–7.78)	0.05	5.99 (2.00–17.92)	0.001
p.Arg168X (52)		3.43 (1.27–9.28)	0.02	3.43 (1.10–10.70)	0.03
p.Arg255X (49)		2.22 (0.85–5.82)	0.10	0.67 (0.17–2.65)	0.56
p.Arg270X (41)		2.36 (0.87–6.41)	0.09	0.83 (0.21–3.36)	0.80
p.Arg294X (49)		4.62 (1.71–12.52)	0.003	2.50 (0.74–8.42)	0.14
p.Arg306Cys (47)		2.01 (0.71–5.70)	0.19	3.70 (1.21–11.31)	0.02
p.Thr158Met (66)		4.76 (1.87–12.10)	0.001	1.79 (0.55–5.84)	0.34
C-terminal deletion (55)		2.41 (0.91–6.37)	0.07	2.17 (0.70–6.74)	0.18
early truncation (26)		2.27 (0.71–7.28)	0.17	2.27 (0.60–8.64)	0.23
other (72)		1.97 (0.77–5.03)	0.16	2.55 (0.89–7.36)	0.08

**TABLE III. The Level of Speech-Language Abilities of Girls Who Did Not Experience a Speech-Language Regression by Type of Mutation (n = 185)**

Mutation (n)	Level of speech-language abilities		
	No speech or language n (%)	Babble n (%)	Words n (%)
large deletion (13)	7 (53.85)	4 (30.77)	2 (15.38)
p.Arg106Trp (9)	5 (55.56)	3 (33.33)	1 (11.11)
p.Arg133Cys (8)	3 (37.50)	1 (12.50)	4 (50.00)
p.Arg168X (26)	13 (50.00)	7 (26.92)	6 (23.08)
p.Arg255X (18)	11 (61.11)	5 (27.78)	2 (11.11)
p.Arg270X (16)	6 (37.50)	8 (50.00)	2 (12.50)
p.Arg294X (12)	6 (50.00)	4 (33.33)	2 (16.67)
p.Arg306Cys (7)	1 (14.29)	3 (42.86)	3 (42.86)
p.Thr158Met (23)	14 (60.87)	6 (26.09)	3 (13.04)
C-terminal deletion (19)	4 (21.05)	4 (21.05)	11 (57.89)
early truncation (18)	7 (38.89)	6 (33.33)	5 (27.78)
other (16)	4 (25.00)	7 (43.75)	5 (31.25)

Our results largely confirmed reported relationships between genotype and aspects of phenotype. For example, in our study girls with the generally considered milder genotypes of p.Arg133Cys [Leonard et al., 2003; Bebbington et al., 2008; Neul et al., 2008] and C-terminal deletion [Neul et al., 2008; Fehr et al., 2011] were more likely to say words before and after speech-language regression, and regress later than those with a mutation associated with a more severe presentation. Interestingly, we found those with a p.Arg168X mutation, generally associated with a more severe presentation of Rett syndrome and the inability to say words [Neul et al., 2008], to be more likely than those with a large deletion to be babbling or saying words after a speech-language regression. This is in keeping with a study that reported two out of 13 girls and women with meaningful speech after regression had a p.Arg168X mutation [Kerr et al., 2006]. Although some relationships between genotype and overall clinical severity are well established [Bebbington et al., 2008; Cuddapah et al., 2014] and generally extend to our findings on speech-language abilities, we unexpectedly found some mutations usually associated with an overall more severe phenotype, such as p.Arg168X [Neul et al., 2008; Cuddapah et al., 2014], to be associated with less severely affected speech-language abilities.

A regression in spoken language is currently required for a diagnosis of typical Rett syndrome [Neul et al., 2010], yet, similar to previous reports, not all of the girls in our investigation experienced such a regression [Uchino et al., 2001; Bartolotta et al., 2011]. We also demonstrated that all types of common *MECP2* mutations were represented in those without a speech-language regression, although those with a C-terminal deletion (11/19, 57.89%) or a p.Arg133Cys (4/8, 50%) mutation made up the largest proportion of girls using words. This finding is similar to our results for the group of girls who did regress in speech-language abilities. Of the girls who did not regress in speech-language abilities, a quarter used words and clinically this group of girls may have been diagnosed with the atypical subtype of Rett syndrome, the persevered speech variant (PSV) [Neul et al., 2010]. Girls and women with speech after the developmental regression period were first described in the 1990s in a series of studies by Zappella [1992, 1994, 1997] and, Zappella and colleagues [1998]. They were described as a group that may possibly represent a unique subtype of Rett syndrome with different underlying aetiology to typical Rett syndrome [Zappella, 1992]. Since this time there have been attempts at developing criteria for the PSV [Renieri et al., 2009; Neul et al., 2010], but these remain largely ambiguous and poorly adopted. Recent studies have used different criteria to define their cases as PSV [Marschik et al., 2009; Marschik et al., 2012] or have failed to clearly state the criteria they used [Marschik et al., 2014]. Furthermore according to the current criteria for PSV it appears that girls who meet the typical criteria for Rett syndrome could be considered as PSV given that the major differential characteristic between these two groups is the presence of recovery of language after developmental regression [Neul et al., 2008]. With this in mind, and given that *MECP2* mutations are found commonly in those with typical Rett syndrome and PSV [Neul et al., 2008], perhaps future research would benefit from considering Rett syndrome as a spectrum disorder with some individuals presenting with more severe features and some with milder features [Bebbington et al., 2008; Neul et al., 2008; Cudda-

pah et al., 2014] rather than trying to define cases as PSV using criteria that at this stage remain largely unclear and inconsistently adopted.

Uncharacteristic presentations of Rett syndrome, including presenting with a late regression in spoken language, are associated with a delayed diagnosis [Fehr et al., 2010]. Receiving a diagnosis is particularly important for families [Knott et al., 2011] and our results can inform clinicians about the variability of the experience of speech-language regression and of speech-language abilities in Rett syndrome. This knowledge, together with accurate assessment of speech-language abilities [Sigafoos et al., 2011] including early speech-language development [Budden, 2012] may facilitate the diagnosis of Rett syndrome in some cases. Findings can also be used to inform parents about clinical features that may be associated with their daughter's specific *MECP2* mutation and in the words of a mother with a daughter with Rett syndrome, give "insight into [their] future" [Knott et al., 2011]. Future research can build on the knowledge available to clinicians and families by describing the speech-language abilities in Rett syndrome using more sensitive measures as well as measuring speech-language abilities longitudinally. Furthermore in terms of extending our knowledge of the development of speech-language abilities it would be useful to compare the abilities of those girls with a regression in speech-language abilities to those who did not experience a speech-language regression as it is likely that such a regression would influence the trajectory of skill development.

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