

# Longevity in Rett Syndrome: Analysis of the North American Database

Russell S. Kirby, PhD, Jane B. Lane, BSN, Jerry Childers, Steve A. Skinner, MD, Fran Annese, LMSW, Judy O. Barrish, BSN, Daniel G. Glaze, MD, Patrick MacLeod, MD, and Alan K. Percy, MD

**Objective** To determine longevity in Rett syndrome (RTT) from a large cohort.

**Study design** The North American RTT Database allows the examination of longevity in a large cohort of individuals with RTT from the United States and Canada. This database contains information on 1928 individuals, 85.5% with typical RTT, 13.4% with atypical RTT, and 1.1% with a mutation in the methyl-CpG-binding protein 2 gene (*MECP2*) but not RTT. Kaplan-Meier analyses were performed to assess longevity.

**Results** Earlier decennial cohorts exhibited better survival than recent cohorts, with most participants surviving into middle age. Comparing overall survival in persons with typical RTT and atypical RTT revealed greater mortality in typical RTT across the observed lifespan ( $P < .0001$ ). Comparing survival in persons with RTT and identified *MECP2* mutations and persons with unknown *MECP2* status demonstrated greater mortality in the latter group ( $P < .0001$ , log-rank test).

**Conclusions** This analysis provides strong evidence for significant longevity in RTT and indicates the need for careful planning for long-term care of these women. The disproportionately greater survival seen in earlier time periods and in persons with atypical RTT may be attributed to more severely affected individuals dying before diagnosis in the former and to greater numbers with milder variants (ie, preserved speech and delayed onset) in the latter. (*J Pediatr* 2010;156:135-8).

Rett syndrome (RTT) is a neurodevelopmental disorder characterized by cognitive impairment, communication dysfunction, stereotypic movement disorder, and growth failure, as first described in 1966 by Andreas Rett.<sup>1</sup> The diagnosis of RTT is based on consensus clinical criteria updated in 2001.<sup>2</sup> More than 200 mutations in the methyl-CpG-binding protein 2 gene (*MECP2*) have been identified, with the 8 most common mutations representing 60% or more of individuals fulfilling the consensus criteria.<sup>3,4</sup> Individuals with RTT are not capable of independent living.

RTT has a prevalence ranging from 1:10-20 000 females. Incidence values are limited, varying from 0.43-0.71/10 000 females in France<sup>5</sup> to 1.09/10 000 females in Australia.<sup>6</sup> Information on longevity is limited. Unpublished observations indicated approximately 70% survival at age 35 in women with RTT, versus 98% in the general female population in the United States (unpublished data, Baylor College of Medicine). Population-based data from Australia showed nearly 78% survival at 25 years in women with RTT versus 99.96% in Australian females generally.<sup>6</sup>

To assess longevity in persons with RTT in the United States and Canada, members of the International Rett Syndrome Association (IRSA) were surveyed.<sup>7</sup> The data collected provide a robust database with respect to diagnosis, mutation status, date of birth, and date of death, if applicable. This report demonstrates the potential for prolonged survival in individuals with RTT and suggests the need for careful planning for long-term care, as well as continued observation of the effects of improved clinical management on longevity.

## Methods

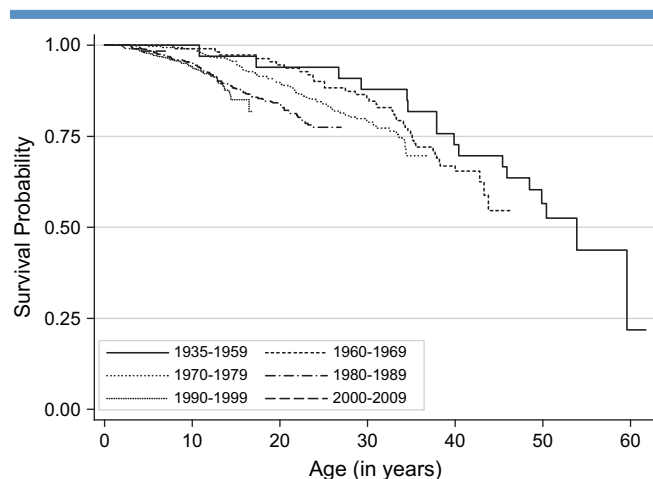
The IRSA mailed a structured survey to 2994 members in the United States ( $n = 2836$ ) and Canada ( $n = 158$ ) requesting specific information, including date of birth, date of death (if applicable), diagnosis (typical RTT, variant or atypical RTT, no RTT, or unknown), discipline of the diagnosing physician, mutation testing results (if performed) and testing laboratory; reason why diagnostic testing was not performed, and contact information (**Appendix**; available at [www.jpeds.com](http://www.jpeds.com)). No response was received from 1439 individuals, a significant number of whom did not receive surveys due to faulty addresses; a total of 1555 (52%) completed surveys were received. Mailing was done by bulk rate routing, which prevented an accurate count of surveys not

From the School of Public Health (R.K.) and Civitan International Research Center (J.L., J.C., A.P.), University of Alabama at Birmingham, Birmingham, AL; Greenwood Genetic Center, Greenwood, SC (S.S., F.A.); Department of Pediatrics, Baylor College of Medicine, Houston, TX (J.B., D.G.); and Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada (P.M.).

Supported by grants from the National Institutes of Health (RR019478) and Mental Retardation Research Center (HD38985), and funds from the International Rett Syndrome Association and Civitan International Research Center. The authors declare no conflicts of interest.

0022-3476/\$ - see front matter. Copyright © 2010 Mosby Inc. All rights reserved. 10.1016/j.jpeds.2009.07.015

IRSA	International Rett Syndrome Association
<i>MECP2</i>	Methyl-CpG-binding protein 2 gene
RTT	Rett syndrome



**Figure 1.** Survival patterns for RTT by decade of birth. Product limit survival function is estimated for 6 separate epochs: 1935-1959, 1960-1969, 1970-1979, 1980-1989, 1990-1999, and 2000-2009. The resulting curves demonstrate the potential for survival into middle age.

reaching their recipients. In addition to the completed surveys, similar data were gathered from the patient databases at Baylor ( $n = 310$ ) and Greenwood Genetic Center ( $n = 28$ ) and from the Canadian RTT database ( $n = 61$ ), following the institutional review board-approved protocol at each institution. After careful redaction of males or participants who failed to meet consensus criteria for RTT and did not have a *MECP2* mutation ( $n = 26$ ), a total of 1928 female participants were included in the survival analyses. For longevity analyses, 21 individuals identified as having a *MECP2* mutation but not RTT were excluded.

All statistical analyses were conducted using SAS version 9.1 (SAS Institute, Cary, North Carolina). Univariate analyses were done using the  $\chi^2$  test and the  $t$ -test for difference of proportions, and SAS PROC LIFETEST was used to generate Kaplan-Meier survival curves. Statistical inference was done with the log-rank test to compare survival curves across strata and the log-rank test and Wilcoxon trend test to examine trends in survival over time. **Figure 1** was generated using Stata/SE version 9.2 (StataCorp, College Station, Texas). The University of Alabama at Birmingham's Institutional Review Board reviewed and approved the research protocol.

## Results

The North American RTT Database comprises individuals who fulfill the criteria for typical or variant RTT or who do not meet these criteria but have a *MECP2* mutation. The diagnosis of RTT is made by a pediatric neurologist, a developmental pediatrician, a geneticist, or a general pediatrician. **Table 1** gives the number of participants and their distribution by diagnosis. This distribution was 85.5% typical RTT, 13.4% atypical RTT, and 1.1% with a *MECP2* mutation but

not fulfilling the criteria for RTT. *MECP2* testing was performed on 1165 individuals (60%); however, the parents were aware of the results in only 1053 of these cases (91%). It was not possible to ascertain the mutation status in 112 individuals whose parents did not know which laboratory performed the test. Of the 1053 individuals for whom mutation results were available, 915 had a mutation (87%). These included 800 of 870 individuals with typical RTT (92%), 94 of 162 individuals with atypical RTT (58%), and 21 of 21 individuals with a *MECP2* mutation but without features of RTT.

Among all of the participants, a total of 305 deaths (15.8%) had occurred as of January 1, 2006. Survival differed significantly between those with typical RTT and atypical RTT (295 deaths/1649 [17.9% mortality] vs 10 deaths/258 [3.9% mortality];  $P < .0001$ ,  $t$ -test for difference of proportions). **Table II** presents the distribution of participants with a diagnosis of typical RTT by decade of birth and by age at death or survival as of January 1, 2006. Examining the distribution of typical RTT and atypical RTT by decade of birth (data not shown) revealed no statistically significant difference ( $P = .14$ ,  $\chi^2$  test, 5 df = 8.32); however, the proportion of atypical RTT appeared to increase over time, rising from approximately 10% in those born before 1970 to approximately 20% in those born after 1999.

**Figure 1** shows survival trends for all participants. Survival patterns differed significantly among the respective groups ( $P < .0003$ , log-rank test), and both the log-rank test for trend and the Wilcoxon trend test were statistically significant ( $P < .0001$ ). The number of individuals available for analysis did not support a decade-by-decade analysis of survival patterns by type of RTT diagnosis or *MECP2* status. Comparing overall survival patterns in participants with typical RTT and those with atypical RTT revealed significantly greater mortality ( $P < .0001$ ) in those with typical RTT at all ages across the observed lifespan (**Figure 2**).

We also found that the individuals with atypical RTT had significantly better survival than those with typical RTT at all ages across the lifespan studied, and that those with identified *MECP2* mutations also had better survival than those with unknown *MECP2* status (data not shown). We also examined survival patterns for participants with atypical RTT related to the presence of an *MECP2* mutation. Although survival did not differ significantly based on *MECP2* mutation status, those with unknown *MECP2* status tended to have increased mortality by age 30 and beyond (data not shown). The

**Table 1.** Participants ( $n = 1928$ ) and *MECP2* mutations in the North American Database by diagnosis

Diagnostic group	Diagnostic distribution (%)	Mutation distribution (%)
Typical	1648 (85.5%)	800/870 (92%)
Atypical	259 (13.4%)	94/162 (58%)
Not RTT ( <i>MECP2</i> positive)	21 (1.1%)	21/21 (100%)

**Table II.** Age at death or survival to January 1, 2006 by decade of birth among cases with typical RTT

Decade of birth	Total cases	Age at death, years							Alive on January 1, 2006	
		1.0-4.9	5.0-9.9	10.0-19.9	20.0-29.9	30.0-39.9	40.0-49.9	50.0+	n	%
1935-1959	30	0	0	2	2	5	5	3	13	43.3
1960-1969	99	0	1	5	10	20	3	0	60	60.6
1970-1979	286	0	3	28	32	9	0	0	214	74.8
1980-1989	511	8	21	63	18	0	0	0	401	78.5
1990-1999	525	13	20	21	0	0	0	0	471	89.7
2000-2005	198	3	0	0	0	0	0	0	195	98.5
Total	1649	24	45	119	62	34	8	3	1354	82.1

available data were insufficient to characterize survival patterns by race/ethnicity.

## Discussion

In this analysis, we examined patterns of RTT survival among individuals in North America born before 1960 to the present. From the most recent period to the earliest period, we found a general pattern of better survival with earlier decade of birth. Given that clinical management has improved considerably from the time when RTT was first recognized, improved survival among each successive cohort might be expected.

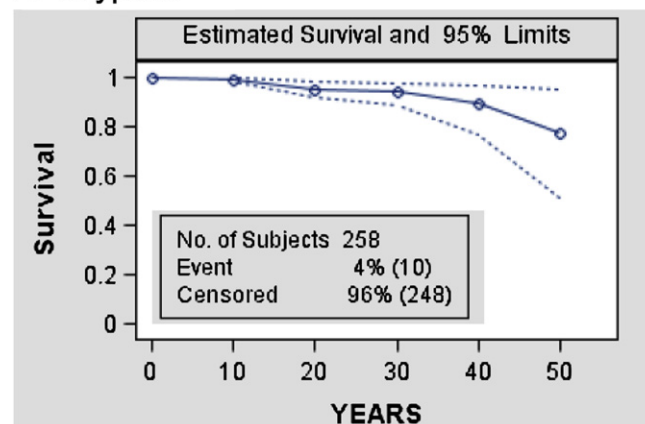
We speculate that the observed pattern may be linked to the increasing availability of molecular genetic testing, which ensures identification of virtually all individuals with RTT within the first decade of life. In previous eras, more severely affected individuals were more likely to escape diagnosis, leading to study populations with greater survival due to milder clinical involvement. Similarly, the disproportionately greater survival seen in individuals with atypical RTT may be attributed to the greater prevalence of milder variants (preserved speech and delayed onset) and decreased prevalence of the early-onset seizure or congenital variants. Again, the more severely affected individuals were more likely to escape diagnosis in earlier eras. We speculate that the poorer survival in participants lacking *MECP2* mutation data might be explained by the greater number of older individuals (who were less likely to undergo genetic testing) in this group, and that the group with known *MECP2* mutations included those with the milder atypical preserved speech and late-onset variants of RTT.

The North American RTT Database represents the first comprehensive compilation of information on individuals with RTT or with another diagnosis in association with an *MECP2* mutation in the United States and Canada. As such, it provides a unique resource for expanding our understanding of RTT and making comparisons with other national databases. The North American RTT Database is derived principally from members of the IRSA, membership in which is voluntary; thus, this database is not population-based. Nonetheless, the large number of participants should be generally representative of individuals with RTT in the United States and Canada. We were unable to examine mortality patterns by cause of death, because of

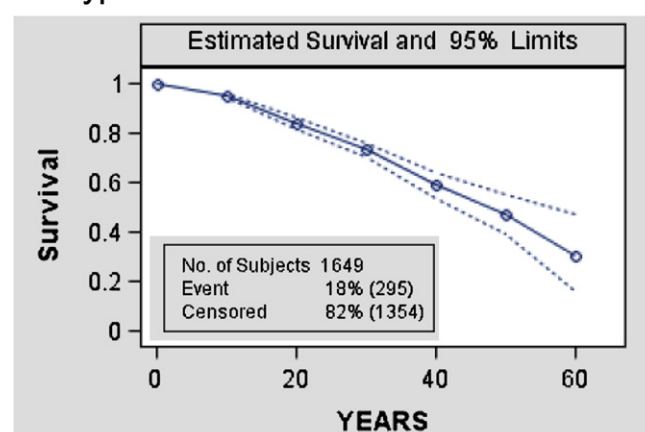
incomplete reporting and the expense involved in using the National Death Index for deaths occurring in the United States.

Although data to assess directly the generalizability of our results are unavailable, our findings are concordant with those of Laurvik et al,<sup>6</sup> who found an overall survival of

### A. Atypical



### B. Typical



**Figure 2.** Overall survival for atypical **A**, and typical **B**, RTT. Kaplan-Meier curves indicate significantly better survival for individuals with atypical versus typical RTT ( $P < .0003$ ; log-rank test). Nevertheless, the potential for survival into middle age is demonstrated for both groups.

approximately 78% at age 25 among females with RTT in the Australian registry. Even though earlier birth cohorts in our study may be incomplete, because more severe cases may have died before diagnosis, it is likely that the study participants born in recent years approximate the North American population with RTT. We recommend the establishment of a population-based North American or US registry, similar to the Australian model, to support future investigations concerning the descriptive epidemiology, genetic/genomic research, health services and outcomes, and clinical interventions for persons with RTT.

This study of longevity in RTT derived from the North American RTT Database provides strong support for the notion of significant longevity in individuals with RTT. In the future, as early diagnosis and clinical management of RTT improve, longevity may be extended even further. As such, our data indicate the need for careful planning for the future care of these women as they advance in years and should raise the level of concern in their parents related to preparing for this future care. The success of this planning needs to be assessed in future studies. ■

*We acknowledge the gracious participation and provision of information by families of the participants and the critical staff support of the IRSA. Dr Mary Lou Oster-Granite, Health Scientist Administrator at the National Institute of Child Health and Human Development, provided invaluable guidance, support, and encouragement for this rare*

*disease initiative. We also thank Jason Salemi, MPH, for his assistance in preparing Figure 1 for publication.*

Submitted for publication Dec 21, 2008; last revision received May 4, 2009; accepted Jul 6, 2009.

Reprint requests: Alan K. Percy, MD, Civitan International Research Center, Room 320E, 1530 3rd Avenue South, Birmingham, AL 35294-0021. E-mail: [apercy@uab.edu](mailto:apercy@uab.edu).

## References

1. Rett A. Über ein eigenartiges hirnatrophisches Syndrom bei Hyperammonämie im Kindesalter. *Wiener Med Wochenschrift* 1966;116:723-6.
2. Hagberg B, Hanefeld F, Percy A, Skjeldal O. An update on clinically applicable diagnostic criteria in Rett syndrome. Comments to Rett Syndrome Clinical Criteria Consensus Panel Satellite to European Paediatric Neurology Society Meeting, Baden Baden, Germany, 11 September 2001. *Eur J Paediatr Neurol* 2002;6:293-7.
3. Amir R, Van den Veyver I, Wan M, Tran C, Francke U, Zoghbi H. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat Genet* 1999;23:185-8.
4. Percy AK, Lane JB. Rett syndrome: model of neurodevelopmental disorders. *J Child Neurol* 2005;20:718-21.
5. Bienvenu T, Philippe C, De Roux N, Raynaud M, Bonnefond JP, Pasquier L, et al. The incidence of Rett syndrome in France. *Pediatr Neurol* 2006;34:372-5.
6. Laurvick CL, de Klerk N, Bower C, Christodoulou J, Ravine D, Ellaway C, et al. Rett syndrome in Australia: a review of the epidemiology. *J Pediatr* 2006;148:347-52.
7. Percy AK, Lane JB, Childers J, Skinner S, Annese F, Barrish J, et al. Rett syndrome: North American Database. *J Child Neurol* 2007;22:1338-41.

**Appendix. International Rett Syndrome Association Longevity Questionnaire**

**IF YOU HAVE NOT RESPONDED TO THIS QUESTIONNAIRE BEFORE**, please answer the following questions regarding your daughter.

Daughter's Full Name: \_\_\_\_\_

1. Diagnosis (check one)

Typical Rett syndrome \_\_\_\_\_

Atypical Rett syndrome \_\_\_\_\_

Unsure or unknown \_\_\_\_\_

2. Diagnosis made by (check all that apply)

Pediatrician \_\_\_\_\_

Neurologist \_\_\_\_\_

Neuropediatrician \_\_\_\_\_

Geneticist \_\_\_\_\_

Other (indicate) \_\_\_\_\_

3. Has *MECP2* genetic testing been completed? Yes or No (circle one)

If "**yes**", give name of lab that performed testing, if known \_\_\_\_\_

4. What was the specific *MECP2* mutation, if known? \_\_\_\_\_ (indicate if "not known")

5. If *MECP2* genetic testing **has NOT** been done, please indicate reason:

Too expensive \_\_\_\_\_

Isn't information we need or want to know \_\_\_\_\_

Didn't know a test was available or don't know what test is \_\_\_\_\_

Wanted test, but physician would not order it \_\_\_\_\_

Other (please indicate) \_\_\_\_\_

6. Has X-chromosome inactivation testing been completed? Yes or No

If "**yes**", give name of lab that performed testing, if known \_\_\_\_\_

7. What were the X-chromosome inactivation results, if known? \_\_\_\_\_ (indicate if "not known")

8. If X-chromosome inactivation testing **has NOT** been done, please indicate reason:

Too expensive \_\_\_\_\_

Isn't information we need or want to know \_\_\_\_\_

Didn't know a test was available or don't know what test is \_\_\_\_\_

Other (please indicate) \_\_\_\_\_

9. Date of birth   /  /  

10. Date of death, if applicable   /   or N/A (circle if not applicable)

11. Cause of death, if applicable and if known. (indicate if "not applicable" or "not known") \_\_\_\_\_

12. Please update **your** contact information.

Parent or Guardian Name: \_\_\_\_\_

Street: \_\_\_\_\_

City: \_\_\_\_\_ State: \_\_\_\_\_ Zip: \_\_\_\_\_

Telephone: \_\_\_\_\_ Alternate telephone: \_\_\_\_\_

Email 1: \_\_\_\_\_ Email 2: \_\_\_\_\_