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# Rett Syndrome: North American Database

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The International Rett Syndrome Association (IRSA) North American database is the first comprehensive compilation of information in the United States and Canada on individuals with Rett syndrome or with another diagnosis in association with *MECP2* mutations. The database contains specific information by diagnosis, mutation status, and mutation type and frequency on 1928 participants. Among the 1928 participants, 85.5% were typical, 13.4% were atypical, and 1.1% had *MECP2* mutations but did not have Rett syndrome. *MECP2* mutations were identified in 914 of 1059 participants (86%): 799 of 870 (92%) participants with typical Rett syndrome had an *MECP2* mutation, 94 of 162 (58%) with atypical Rett syndrome had a mutation, and all 21 individuals diagnosed as Not Rett syndrome had a

mutation. Missense-type mutations (39.0%) were slightly more common than nonsense type (35.1%). Individual mutation frequency for the 8 common mutations varied from 11.9% for T158M to 4.4% for R106W; large deletions accounted for 6.4% and C-terminal truncations occurred in 8.8%. The remaining mutations (14.3%) occurred singly or in small numbers. This database provides a unique resource for expanding our understanding of Rett syndrome, for comparison with other national databases, and for future study including organization of clinical trials based on the expected emergence of fundamental therapies.

**Keywords:** Rett syndrome; *MECP2*; mutations; genetics

Rett syndrome, a neurodevelopmental disorder characterized by cognitive impairment, communication dysfunction, stereotypic movement disorder, and growth failure, was first described in 1966 by Andreas Rett.<sup>1</sup> The diagnosis of Rett syndrome requires fulfillment of consensus clinical criteria established in 2001.<sup>2</sup> Mutations in the *MECP2* (methyl-CpG-binding protein 2) gene were identified in females meeting these diagnostic criteria.<sup>3</sup> At present, more than 200 mutations have been identified in *MECP2*, although 8 common mutations are found in 60% or more of those fulfilling consensus criteria.<sup>4</sup>

Rett syndrome occurs in all ethnic groups across the world. Prevalence rates range from 1:10 000 to 1:20 000 females, exceeding that for phenylketonuria. Incidence values vary from 0.43 to 0.71/10 000 females in France<sup>5</sup> to 1.09/10 000 females in Australia.<sup>6</sup> Information regarding longevity is scarce. Unpublished reports suggest normal survival to age 10 and approximately 70% survival at age 35 versus 98% in

the general female population in the United States. Data from Australia indicate nearly 78% survival at 25 years versus 99.96% in Australian females generally.<sup>6</sup>

To provide similar information from the United States and Canada, members of the International Rett Syndrome Association (IRSA) were surveyed. In the process a robust database has been developed regarding diagnosis, mutation status, and specific information on mutation type and frequency. In this report, we describe the IRSA North American database and compare the findings with existing compilations.<sup>7-16</sup>

## Methods

IRSA mailed a structured survey to 2994 members in the United States (2736) and Canada (158) requesting specific information including date of birth, diagnosis (typical Rett syndrome, variant or atypical Rett syndrome, not Rett syndrome, or unknown), mutation testing, and testing results, if performed. We had no responses from 1439, yielding 1555 (52%) completed surveys. Of the 1439, we are aware from direct contact and e-mail inquiries that a significant number of surveys were not received because of faulty addresses. Because the mailings were conducted via bulk rate routing, we do not have an accurate count of surveys actually received. In addition, similar data were gathered from the patient databases at Baylor College of Medicine (n = 310) and Greenwood Genetic Center (n = 28) and from the Canadian

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**Table 1.** Distribution of Participants in North American Database by Diagnosis

Total enrolled	1928
Typical	1648 (85.5)
Atypical	259 (13.4)
Not RS ( <i>MECP2</i> positive)	21 (1.1)

NOTE: RS = Rett syndrome. Values are n (%).

**Table 2.** *MECP2* Testing Status for Participants in Database

Total enrolled	1928
Tested	1165 (60)
Not tested	763 (40)
<i>MECP2</i> not known	869 (45)
Tested, known	1059 (91)
Tested, not known	106 (9)
Tested, mutation	914 (86)
Tested, no mutation	145 (14)

Values are n (%).

Rett syndrome database (n = 61), each of which are part of institutional review board–approved protocols at the respective institutions. After careful editing to remove males or participants who failed to meet consensus criteria for Rett syndrome and did not have an *MECP2* mutation (n = 26), 1928 female participants were included in the following analyses.

## Results

Participants who fulfilled criteria for Rett syndrome, either typical or one of the variant forms, and who did not meet criteria but had a mutation in *MECP2*, the gene associated with Rett syndrome, compose the North American database. All diagnoses were made by a physician: a pediatric neurologist, a developmental pediatrician, a geneticist, or a general pediatrician. The total number of participants and the distribution by diagnosis are displayed in Table 1. Of the 1928 participants included in this analysis, 85.5% were typical, 13.4% were atypical, and 1.1% had *MECP2* mutations but did not have Rett syndrome.

Among the 1928 participants, 1165 (60%) had *MECP2* testing (Table 2). Of these, mutation results were known by the parents in 1059 (91%), and *MECP2* mutations were identified in 914 of 1059 (86%). When mutation status was stratified by diagnosis (Table 3), among participants with typical Rett syndrome, 799 of 870 (92%) had an *MECP2* mutation, 94 of 162 (58%) with atypical Rett syndrome had a mutation, and all 21 individuals diagnosed as Not Rett syndrome had a mutation.

**Table 3.** *MECP2* Mutation Status for Participants in Database

Group	Total	Mutation	No mutation	Unknown
Typical	1648	800 (92)	70 (8)	778
Atypical	259	94 (58)	68 (42)	97
Not RS	21	21 (100)	0	0

NOTE: RS = Rett syndrome. Values are n (%).

**Table 4.** Distribution of *MECP2* Mutations for Participants in Database

Mutation	No.	%	RettBase %
T158M	109	11.9	9.1
R168X	86	9.4	8.8
R255X	83	9.0	7.9
R270X	66	7.2	6.9
R306C	63	6.9	4.6
R133C	59	6.4	4.4
R294X	57	6.2	5.6
R106W	40	4.4	3.4
Large deletions	59	6.4	Not reported
C-terminal truncations	81	8.8	Not reported
Other deletions	58	6.3	Not reported
Insertions	26	2.8	Not reported
All others	131	14.3	Not reported

**Table 5.** *MECP2* Mutation Type for Participants in Database

Mutation Type	No.	%
Missense	358	39.0
Nonsense	323	35.1
Frameshift	178	19.4
Complex deletion	59	6.4

Table 4 details the distribution of mutations. Among the 8 known common mutations, individual mutation frequency varied from 11.9% for T158M to 4.4% for R106W. Large (complex) deletions accounted for 6.4%, C-terminal truncations occurred in 8.8%, and the numerous remaining mutations (identified singly or in small numbers) made up 14.3%.

Mutation type is detailed in Table 5. The frequency of missense (39.0%) and nonsense (35.1%) mutations was quite similar. The remaining mutations were composed of frameshift insertions or deletions (19.4%) and complex deletions (6.4%).

## Discussion

The IRSA North American database is the first comprehensive compilation of information on individuals with

**Table 6.** Comparative Distribution of *MECP2* Mutations by Location and Type

Mutation	Present Study (n = 918) <sup>a</sup>	RettBase <sup>b</sup> (n = 2110)	United States <sup>7</sup> (n = 99)	Spain <sup>8</sup> (n = 47)	Italy & United Kingdom <sup>9</sup> (n = 43)	Denmark <sup>10</sup> (n = 26)	Germany <sup>11</sup> (n = 97)	China <sup>12</sup> (n = 17)	France <sup>13</sup> (n = 191)	France <sup>14</sup> (n = 424)	Italy <sup>15</sup> (n = 162)	Czech Republic <sup>16</sup> (n = 68)
T158M	11.9 <sup>c</sup>	8.6	21.2	17.0	16.3	11.5	8.2	23.5	7.8	8.3	8.0	16.2
R168X	9.4	8.6	13.1	14.9	11.6	11.5	13.4	11.8	11.5	11.5	8.0	4.4
R255X	9.0	7.5	12.1	21.3	16.3	15.4	10.3	5.9	11.0	8.7	9.9	7.4
R270X	7.2	6.5	8.1	2.1	7.0	3.8	9.3	0	10.5	9.0	9.3	4.4
R306C	6.9	4.2	8.1	4.3	2.3	7.7	3.1	11.8	6.8	6.8	6.8	7.4
R133C	6.4	4.1	3.0	8.5	11.6	3.8	6.2	5.9	3.1	4.2	6.8	10.3
R294X	6.2	5.4	7.1	6.4	2.3	11.5	7.1	5.9	5.2	5.9	5.6	5.9
R106W	4.4	3.2	3.0	4.3	2.3	3.8	3.0	0	5.2	4.2	1.2	7.4
Large deletion	6.4	NA	NA	NA	NA	NA	NA	NA	14.0	5.8	9.9	2.9
Missense	39.0	24.0	38.4	38.3	37.2	30.8	35.0	47.1	36.0	35.6	32.7	50.0
Nonsense	35.2	32.2	45.5	44.7	44.2	50.0	49.5	23.5	41.0	37.3	34.0	26.5

NOTE: NA = not available.

a. Values in parentheses are number of mutations per study.

b. [www.mecp2.chw.edu.au](http://www.mecp2.chw.edu.au)

c. Values in the table are frequency of mutations in percentages.

Rett syndrome or with another diagnosis in association with *MECP2* mutations in the United States and Canada. As such, the database provides a unique resource for expanding our understanding of Rett syndrome and for comparison with other national databases. The North American database is derived principally from members of IRSA, in which membership is voluntary. Therefore, this database is not population-based. Nonetheless, the large number of participants should be generally representative of Rett syndrome within the United States and Canada.

The diagnosis of Rett syndrome is based on fulfilling consensus criteria for typical or variant forms. Inasmuch as *MECP2* mutations are not identified in all individuals meeting these criteria and similar mutations are also identified in individuals who do not meet these criteria, the diagnosis of Rett syndrome is based on clinical assessment. The distribution of typical (85.5%) and atypical (13.4%) Rett syndrome among the participants mirrors that reported in Sweden.<sup>17</sup> Comparative data for individuals with *MECP2* mutations but not meeting consensus criteria are lacking. Such participants in this database, representing 1.1% of the total, are likely to underestimate the actual frequency in the general population because of failure to assess mutation status in the absence of features suggestive of Rett syndrome.

Only 60% of participants had been tested for *MECP2* mutations. In general, those born before 1990 were much less likely to have had such testing performed. Parents of these older participants were very comfortable with the clinical diagnosis. For them, the diagnosis of Rett syndrome had been made well before gene testing became available, and they saw no reason to pursue additional testing. In addition, in many instances they could not afford the testing. In nearly 10% of participants who had been tested, the specific results were not known to the

parents nor did they know where the testing had been performed. Again, because they were comfortable with the clinical diagnosis, they had not pursued this information.

When mutation frequency was analyzed based on clinical diagnosis, not surprisingly, the likelihood of finding an *MECP2* mutation was greater in participants with typical Rett syndrome (92%) versus atypical (58%). The value for typical Rett syndrome approaches the currently accepted figure of ~95% when complete testing is performed. In this study group, some participants had been tested prior to the identification of exon 1 mutations and complex rearrangements that would be missed by routine sequencing methodologies. Again, the parents of those individuals with negative sequencing test results had not pursued additional *MECP2* testing in some instances because they were unaware of its availability or in others for financial reasons.

The distribution of *MECP2* mutations among the 914 participants with positive testing is similar to published data, in particular the larger series from France and Italy and those recorded in RettBase ([www.mecp2.chw.edu.au](http://www.mecp2.chw.edu.au)). In total, 918 mutations were identified among the 914 participants; 2 participants had 2 different common mutations and 1 participant had 2 common mutations as well as a deletion. For the 8 most common mutations, T158M was observed most frequently in this study, whereas R168X occupied this position in both reports from France. With regard to RettBase, the rank order was virtually identical to that in this study. Aside from studies from China, the Czech Republic, and this study, nonsense mutations were generally more common. With the exception of China and the Czech Republic, the overall regional differences are rather minor.

The North American Rett syndrome database provides a resource for future study including the examination of longevity in Rett syndrome. Although we anticipate that mutation testing will be common in the future, we

strongly encourage complete *MECP2* testing when the clinical diagnosis of Rett syndrome is made, including those older individuals who have had no previous mutation analyses or whose previous sequencing was negative and expanded testing was unavailable or not pursued. With the expected emergence of fundamental therapies, such testing will be required for entry into clinical trials.

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