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Rett Syndrome: Recent Research Progress

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Recent progress in our understanding of Rett syndrome has been dramatic. Against the background that the clinical features of Rett syndrome may be reversible, in part or in whole, substantial optimism has emerged regarding possible therapies. As such, it is timely to update recent research progress. This update summarizes research advances during the past 18 to 24 months in terms of clinical and translational research, as well as basic research.

Keywords: Rett syndrome; research progress; *MECP2*; mutations; mouse models

Recent progress in our understanding of Rett syndrome has been dramatic. Notable optimism has emerged regarding possible therapies relative to the background that the clinical features of Rett syndrome may be reversible, in part or in whole. Under the auspices of the International Rett Syndrome Association, the recent compilation of the North American Database[1] of patients with Rett syndrome will be beneficial to the process of launching clinical trials. In brief, the North American Database, derived principally from members of the International Rett Syndrome Association, represents the first comprehensive compilation of information in the United States and Canada on individuals with Rett syndrome or with another diagnosis in association with an *MECP2* mutation. The North American Database contains specific information by diagnosis, mutation status, and mutation type and frequency on 1928 participants. Among 1928 cases, 85.5% were typical, 13.4% were atypical, and 1.1% had *MECP2* mutations but did not have Rett syndrome. *MECP2* testing has been completed in 1165 subjects, for whom results are known in 1059 (90.9%). Overall, *MECP2* mutations were identified in 914 of 1059 subjects (86.3%), but when stratified by diagnosis, 799 of 870 subjects (91.8%) with typical Rett syndrome had an *MECP2* mutation, 94 of 162 subjects (58.0%) with atypical Rett syndrome had an *MECP2* mutation, and all 21 subjects whose diagnosis was not Rett syndrome had an *MECP2* mutation. Missense-type mutations (39.0%) were slightly more common than nonsense-type mutations (35.1%). Individual frequencies 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 expansion of our understanding of Rett syndrome, for comparison with other national databases, and for future study, including clinical trials based on the expected emergence of fundamental therapies. This update summarizes research advances during the past 18 to 24 months in terms of (1) clinical and translational research and (2) basic research.

Clinical and Translational Research

Diagnostic Strategies

How do molecular diagnoses change the definition or categorization of specific disorders such as Rett syndrome? Although a molecular definition might be appropriate, many single-gene disorders are associated with multiple phenotypes, as occurs in Rett syndrome, suggesting that molecular categorization is not advisable at this time.[2]

Since the identification of mutations in exon 1 and of large deletions of *MECP2*, more than 95% of individuals fulfilling consensus criteria for Rett syndrome will have an identifiable pathogenic mutation. Large deletions represent 6% to 10% of the total cases. Exon 1 mutations account for only about 1%, as recently confirmed.[3] Identification of an *MECP2* control region mutation that blocks the normal coupling of coding information for this gene and results in an absence of MeCP2 protein provides yet another mechanism that would escape diagnostic detection by standard laboratory methods. Application of this method to individuals meeting Rett syndrome diagnostic criteria but lacking a mutation by standard diagnostic testing may provide additional sensitivity to molecular confirmation.[4]

The following 5 country-specific reports indicate global expansion of *MECP2* testing. (1) In Korea, mutations were identified in 26 of 43 (60.5%) children (41 girls and 2 boys)

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