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Rett syndrome genetic variants now available for advance testing, diagnosis and research

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Despite the identification of gene mutations in methyl CpG binding protein 2 (MECP2) being linked to Rett syndrome (RS), research has been hindered by the lack of commercially available reference materials. Through collaboration between the Centers for Disease Control and Prevention (CDC) and members of the clinical-laboratory and non-profit–research communities, 35 DNA samples containing many common RS genetic variants have now been characterized and made publicly available, eliminating a major stumbling-block for investigators and opening the possibility of earlier, more accurate diagnosis of Rett syndrome, reports *The Journal of Molecular Diagnostics*.

The study was conducted via the CDC Genetic Testing Reference Materials Coordination Program (GeT-RM), which aims to help the genetic testing community obtain appropriate and well-defined reference materials for inherited genetic disorders, including cancer and infectious diseases. Researchers selected eight cell lines from RS patients already available from the National Institute of General Medical Sciences' Coriell Cell Repository, which contained six of the most common mutations that cause RS, as well as one additional point mutation. In addition, DNA was obtained from 27 newly established cell lines derived from blood samples from Rett patients, which included a number of other MECP2 variants. Two of the samples were from males.

The samples were sent for DNA sequence and deletion/duplication analyses (using MLPA, semi-quantitative PCR, or array) to College of American Pathologist–accredited clinical genetic testing laboratories,

and each sample was tested in between two to five laboratories. The investigators found that the results were concordant among laboratories and assay platforms.

"The panel of 35 publicly available genomic DNA samples developed and characterized as part of this study contains a wide variety of point mutations, deletions, and duplications in both male and female samples that can be used by clinical laboratories to ensure the quality of Rett syndrome testing," asserts Dr. Kalman.

Point mutations or deletions/insertions of the MECP2 gene, which regulates aspects of brain development as well as the expression of other genes, were discovered to be associated with most cases of RS in 1999. However, since there are still no FDA-approved assays for Rett syndrome, laboratories have developed their own tests but need reference materials to standardize their techniques, validate assays, and meet regulatory and accreditation requirements. Ideally, the reference materials should be well characterized and contain the variants most commonly seen in RS patients.

"The availability of a renewable source of characterized reference materials for Rett syndrome will help to ensure the accuracy of these genetic tests and facilitate research and test development," comments Lisa Kalman, PhD, of the Division of Laboratory Programs, Standards, and Services at the Centers for Disease Control and Prevention.

"Molecular diagnosis of Rett syndrome is performed by examination of patient DNA for MECP2 mutations using a variety of molecular diagnostic methods," explains Dr. Kalman. "Genetic testing can help to confirm or establish the diagnosis of RS, especially when patients are young and the phenotype may not be completely apparent. Testing may also be important for at-risk relatives, prenatal diagnosis, or evaluation of an embryo prior to implantation during in vitro fertilization."

Rett syndrome, a dominant X-linked neurodevelopmental disorder that primarily affects girls, occurs in one of every 10,000 to 15,000 live births. Girls with RS first appear to grow and develop normally, but between the ages of 1 and 4 years start to exhibit development delays, loss of purposeful use of the hands, slowed brain and head growth, and motor difficulties. In later stages, affected individuals may develop a spectrum of symptoms with varying severity, including muscle weakness, rigidity, spasticity, abnormal posturing, inability to speak, seizures, and repetitive hand movements such as wringing or washing.

More information: "Development of a genomic DNA reference material panel for Rett Syndrome (MECP2-related disorders) genetic testing," by Lisa V. Kalman; Jack C. Tarleton; Alan K. Percy; Swaroop Aradhya; Sherri Bale; Shannon D. Barker; Pinar Bayrak-Toydemir; Christina Bridges; Arlene M. Buller-Burckle; Soma Das; Ramaswamy K. Iyer; Timothy D. Vo; Val V. Zvereff; and Lorraine H. Toji, dx.doi.org/10.1016/j.jmoldx.2013.11.004 .The *Journal of Molecular Diagnostics*, Volume 16, Issue 2 (March 2014)

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