Molecular pathology of Rett syndrome

Abstract

Rett syndrome (RTT) is a severe X-linked neurodevelopmental disorder affecting almost exclusively females. It is characterized especially by psychomotor regression, loss of acquired speech and purposeful hand skills, acquired microcephaly, repetitive stereotypic hand movements, and epileptic seizures. Most of RTT cases are caused by de novo mutations in the MECP2 gene encoding a methyl-CpG-binding protein 2 (MeCP2). The MeCP2 protein plays an important role in regulation of gene expression, chromatin remodeling, and is also involved in RNA splicing. More severe atypical RTT variants (early-onset seizure and congenital variant) may also be caused by mutations in other genes, such as CDKL5 or FOXG1.

The Laboratory for study of mitochondrial disorders at Department of pediatrics and adolescent medicine is the only center of DNA diagnostics of RTT in Czech Republic. Therefore, the thesis was focused especially on improving the molecular diagnostics according to the recent research progress. We established the analysis of large deletions and duplications by multiplex ligation-dependent probe amplification (MLPA). Combining the sequencing and MLPA analysis of the MECP2 gene we confirmed the causative mutations in 80 patients. 11 mutations were novel. Mutation analysis of the CDKL5 gene, the main causative gene in atypical RTT with early-onset seizures, was established and also become available for patients with early epileptic encephalopathy 2. We optimized and validated a rapid and cost-effective screening method, high-resolution melting analysis, for both genes.

Clinical manifestations and severity of RTT caused by MECP2 mutations are widely variable. They mostly depend on type and position of MECP2 mutation and X chromosome inactivation status (XCI). Since these factors often cannot interpret all RTT cases, other modulation factors must be considered. Our results confirm that certain MECP2 mutation types usually lead to milder or more severe clinical phenotypes. We also selected and analyzed several candidate modulation genes and show that especially allele ε4 of APOE gene should be taken into consideration. It was associated with significantly earlier onset of psychomotor regression in our confirmed RTT patients.

Understanding the relationship between clinical manifestation and modulation factors in addition to different MECP2 mutations will shed more light into RTT pathogenesis. It may help to predict possible evolution of clinical features in a certain patient as well as to assist in planning a specific supportive therapy.