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Detection, Analysis and Determination of the Origin of Copy Number Variants (CNVs) in Intellectual Disability/Developmental Delay (ID/DD) Patients and Autistic Spectrum Disorders (ASD) Patients by Molecular and Cytogenetic Methods

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Abstract : ASDs are heterogeneous and complex developmental diseases with a significant genetic background. Recurrent CNVs are known to be a frequent cause of ASD. These CNVs can have, however, a variable expressivity which results in a spectrum of phenotypes from asymptomatic to ID/DD/ASD. ASD is associated with ID in ~75% individuals. Various platforms are used to detect pathogenic mutations in the genome of these patients. The performed study is focused on a determination of the frequency of pathogenic mutations in a group of ASD patients and a group of ID/DD patients using various strategies along with a comparison of their detection rate. The possible role of the origin of these mutations in aetiology of ASD was assessed. The study included 35 individuals with ASD and 68 individuals with ID/DD (64 males and 39 females in total), who underwent rigorous genetic, neurological and psychological examinations. Screening for pathogenic mutations involved karyotyping, screening for FMR1 mutations and for metabolic disorders, a targeted MLPA test with probe mixes Telomeres 3 and 5, Microdeletion 1 and 2, Autism 1, MRX and a chromosomal microarray analysis (CMA) (Illumina or Affymetrix). Chromosomal aberrations were revealed in 7 (1 in the ASD group) individuals by karyotyping. FMR1 mutations were discovered in 3 (1 in the ASD group) individuals. The detection rate of pathogenic mutations in ASD patients with a normal karyotype was 15.15% by MLPA and CMA. The frequencies of the pathogenic mutations were 25.0% by MLPA and 35.0% by CMA in ID/DD patients with a normal karyotype. CNVs inherited from asymptomatic parents were more abundant than de novo changes in ASD patients (11.43% vs. 5.71%) in contrast to the ID/DD group where de novo mutations prevailed over inherited ones (26.47% vs. 16.18%). ASD patients shared more frequently their mutations with their fathers than patients from ID/DD group (8.57% vs. 1.47%). Maternally inherited mutations predominated in the ID/DD group in comparison with the ASD group (14.7% vs. 2.86 %). CNVs of an unknown significance were found in 10 patients by CMA and in 3 patients by MLPA. Although the detection rate is the highest when using CMA, recurrent CNVs can be easily detected by MLPA. CMA proved to be more efficient in the ID/DD group where a larger spectrum of rare pathogenic CNVs was revealed. This study determined that maternally inherited highly penetrant mutations and de novo mutations more often resulted in ID/DD without ASD in patients. The paternally inherited mutations could be, however, a source of the greater variability in the genome of the ASD patients and contribute to the polygenic character of the inheritance of ASD. As the number of the subjects in the group is limited, a larger cohort is needed to confirm this conclusion. Inherited CNVs have a role in aetiology of ASD possibly in combination with additional genetic factors - the mutations elsewhere in the genome. The identification of these interactions constitutes a challenge for the future. Supported by MH CZ – DRO (FNOl, 00098892), IGA UP LF_2016_010, TACR TE02000058 and NPU LO1304.

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