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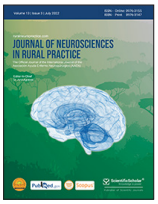

Letter to Editor

Results of a genetic study of children with Duchenne myodystrophy in Kazakhstan

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Dear Editor,

The study involved 106 boys aged from 2 to 18 years. All the boys had complaints of muscle weakness, fatigue, and various gait disorders. We used methods such as molecular methods of multiplex-ligase-dependent probe amplification (MLPA) and next-generation sequencing (NGS) of the Duchenne muscular dystrophy (*DMD*) gene. To study the clinical features, we used the P.J.Vignos scale of functional motor activity of the lower extremities and the 6-min walking test (6MWT). The diagnosis was verified based on the current clinical protocols for the diagnosis and treatment of DMD. All patients underwent a comprehensive clinical and neurological examination. Informed consent was obtained from each patient (parent). Permission to conduct the study was obtained from the Local Bioethics Commission at the West Kazakhstan Medical Marat Ospanov No.24 dated May 17, 2019. Session No. 4.

To analyze mutations in the gene, all children underwent MLPA (MRC-Holland, Amsterdam, the Netherlands) using SALSA 034 and SALSA 035 probe reagents. The material was processed using the ABI PRISM 3100 genetic analyzer (Applied Biosystems, USA). For children with a negative MLPA result, an NGS analysis was performed to search for point mutations. The *DMD* gene is usually analyzed by next-generation amplicon-based sequencing. Amplicons cover the entire coding region and highly conserved exon-intron junctions.[1,2] Minimum coverage >20× for each amplicon and technical sensitivity (single nucleotide variant/InDels) 99.9%. Variation of the number of copies included allows the detection of deletions and duplications using the NGS methodology.[3]

The search for genetic mutations was primarily carried out by the MLPA method. Large mutations in the form of deletions and duplications were verified in 75 cases (70.7%). In MLPA negative patients, further search for point mutations was carried out by gene sequencing, where point mutations were verified in 31 children (29.3%). Thus, DMD was genetically verified in 106 patients. The resulting mutation types are distributed as follows: major deletions 61 (57.5%), major duplications 14 (13.2%), and point mutations 31 (29.3%). The severity and progression of the disease in many cases depend on the type of mutation and the state of the translational reading frame.[4,5] In our work, the evaluation of this reading frame was carried out in 93 cases, where in 55 cases (59.1%), the reading frame is shifted, in 38 cases (40.9%), the translational frame is preserved. Various clinical features were identified according to various criteria. The average age of non-outpatient is 9.5 ± 0.25 years. The indicator of a 6-min walk averaged 390.97 ± 16.8 m. When comparing the results of the 6MWT, the average figures of the distance of independent walking are significantly lower in the group of children with the type of mutation shifting the reading frame.[6] To assess the role of mutation with a shift in the translational framework, 37 children were evaluated, whose indicator was 2 or more times less than the norm, that is, 250 m.

The distribution of children with Duchenne myodystrophy in the context of the reading frame and the Vignos scale showed that, while maintaining the translational reading frame, the average values varied at the level of 20.0% ± 17.8% in class 5, in contrast to children of this class with a violation of the translational reading frame of 80.0% ± 17.8%, which is almost 4 times higher ($P \leq 0.05$).

According to the results of molecular diagnostics, large deletions were detected in 61 cases (57.5%), large duplications in 14 cases (13.2%), point mutations in 31 patients (29.3%). The identified mutations in the hot spots (45–55 exons) in our study amounted to 34.9%, while mutations in the proximal part of the gene and in the distal part of the gene amounted to 39.6% and 25.5%, respectively. The reading frame was

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evaluated in 93 cases, where in 55 cases the reading frame is shifted, and in 38 cases the translational frame is preserved. According to the results of the 6MWT test, in children (37) mutations with a shift in the translational frame, the indicator was 2 or more times less than the norm, that is, 250 m. The assessment of the Vignos scale and the reading frame showed that while maintaining the translational reading frame, the average values varied at the level of 20.0% ± 17.8% for class 5, in children of this class with a violation of the translational reading frame of 80.0% ± 17.8%, which is almost 4 times higher. The early onset of the disease depended on a violation of the translational framework in 70.59% (the value exceeds 2.4 times), in children without a violation of the translational framework in 29.41% of cases.

In our work, we studied the correlative relationships of the main clinical data with various characteristics of mutations, where the analysis of the results shows a clear statistically significant reliable association of early loss of independent movement, early onset of the disease with mutations that can disrupt the translational reading frame of the dystrophin protein. Taking into account the fact that of the groups of genetic diseases, the most urgent problem of clinical neurology is neuromuscular diseases.[7,8]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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