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The spectrum of mutations in the *EXT1* gene among patients with Multiple Hereditary Exostoses in the Republic of Sakha (Yakutia)

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Motivation and Aim: Multiple hereditary exostoses (MHE) or multiple osteochondromas (MO) (OMIM 133700, OMIM 133701) is a genetically heterogeneous disease with an autosomal dominant mode of inheritance. The most common cause is mutations in the *EXT* genes, which are responsible for at least 70 % of all cases of MHE. Three loci of the *EXT1*, *EXT2*, and *EXT3* genes have been described, mapped at 8q24, 11p12, and 19p respectively. Mutations in the *EXT2* gene are three times less common than in the *EXT1* gene; only a few descriptions are known for the *EXT3* locus [1]. MHE intensively develops during the period of physiological growth of the skeleton, in childhood and adolescence, it is represented by generalized forms of skeletal damage with numerous progressive deformities of bones and joints, shortening and secondary changes in bones, which can cause clinical, socio-psychological problems that affect the quality of life of the patient [2, 3]. Exostoses cause compression of large vessels and nerves, which requires repeated surgical intervention to remove them during the period of growth and development of the organism [4, 5].

On the territory of Russia, studies of the molecular genetic cause of MHE are rare, and in the Republic of Sakha (Yakutia) such studies have not been carried out. Therefore, the study of multiple hereditary exostoses in Yakutia is both a fundamental scientific problem and a medical and social task for diagnosing, preventing and predicting the course of this hereditary disease. This paper presents the results of a molecular genetic study to search for mutations in the *EXT1* gene among patients with MHE in Yakutia.

Materials and Methods: Molecular genetic study was carried out among 57 patients with MHE. For verification and validation of molecular genetic analyzes, DNA extraction, polymerase chain reaction, clinical exome sequencing on a high-performance MiSeq sequencer (Illumina, USA) using a Trusight One Sequencing panel (Illumina, USA) and Sanger sequencing were used. Variant Studio 3.0 programs, ExAC, 1000G and ESP6500 bases were used for bioinformatic analysis, and SIFT, PolyPhen2, MutationTaster software tools were used to check the functional significance *in silico*.

Results: Only 8 mutations were found in the *EXT1* gene, of which were previously published: in exon 1, c.854dupA (p.His285Glnfs*4); in intron region 9, c.1883+2T > A; in exon 11, c.2101C > T (p.Arg701*); previously unreported: in exon 2 – c.970delT (p.Tyr324Phefs*35), c.1003delC (p.Leu335Trpfs*24), c.1019G > A (p.Arg340His); in exon 4, c.1171delT (p.Ser391Leufs*12), in exon 8, c.1703_1713delCGGTGCTTTCA

(p.Thr568Asnfs*16). According to the results of the study, mutations in the *EXT1* gene were found in 22.8 % of the examined patients.

Conclusion: The results of this study made it possible to expand the pathological spectrum of mutations in the *EXT1* gene and to establish the etiology of the MHE disease. New data have been obtained, which can be further used in the diagnostic program of patients with MHE.

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