METHATROPIC DYSPLASIA: CLINICAL AND MOLECULAR DIAGNOSTICS, GENETIC COUNSELING

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Metatropic dysplasia (MTD; OMIM #156530) is a rare spondyloepimetaphyseal dysplasia with autosomal dominant inheritance. Here we present the results of the clinical, radiological and molecular genetic diagnosis of MTD in a Circassian girl with novel de novo p.Pro82Leu (NG_017090.1:g.23856C>T, c.245C>T) mutation in exon 1 of the TRPV4 gene. Considering gonadal mosaicism prenatal diagnosis in MTD families for the next pregnancies is recommended.

Key words: genetic epidemiology, metatrophic dysplasia, TRPV4 gene, mutation de novo
The whole gene TRPV4 activation results in skeletal dysplasia. Oligonucleotides were synthesized by Evrogen Inc., Moscow, Russian Federation.

Bidirectional sequencing of PCR fragments was performed with BigDye Terminator v1.1 Cycle Sequencing Kit on the 3130xL Genetic Analyzer (Applied Biosystems, Foster City, CA). The frequency of identified allele in general population was established based on the Database of Single Nucleotide Variants (dbSNP, http://www.ncbi.nlm.nih.gov/snp/) and the ExAC browser (http://exac.broadinstitute.org/). The predicted functional effect of the missense variant was determined through PolyPhen, MutationTaster, MutationAssessor. A test system was developed for the screening of detected mutation in 50 healthy Circassians. Forward primer 5'-GACTCCAGCAAGATCAGCTG-3' with one nucleotide mismatch forms a restriction site for Ddelendonuclease in the mutant allele (reverse primer: 5'-GAGGCTTTTCTTCTTCTC-3').

Results and Discussion. A Circassian family with MTD was revealed in the course of hereditary diseases study in Khabezsky District of Karachaevo-Cherkess Republic (Northern Caucasus Region, Russian Federation).

For the first time 1,5-year-old girl was referred with MTD at the Turner Scientific Research Institute for Children’s Orthopedics in St Petersburg in 2014. The diagnosis of MTD was confirmed during clinical and radiography examination at the Central Research Institute of Traumatology and Orthopaedics of N.N. Priorov. At the age of two the child died from pneumonia.

The proband was the first child of healthy non-consanguineous parents after an unremarkable pregnancy at term. Mother’s age at time of the child birth was 21 and father’s 27 years old. There was no family history of a skeletal dysplasia.

By the clinical examination time progressive kyphoscoliosis, distortion and bowing of the limbs, muscle hypotonia, movement constriction in large joint and deformed narrow chest were diagnosed (Fig. 1). Face dismorphisms included frontal bossing and midface hypoplasia.

Radiology examination showed: kyphoscoliosis; decreased bone density; marked platyspondyly; horizontally elongated thoracic vertebrae, squared-off lumbar vertebrae; shortened and tortuous clavicles; deformed, laterally impacted thorax, hypoplastic in its upper segments; flattened and enlarged in their anterior parts ribs; halberd shaped pelvis; constriction between ilium corpus and ala; bowing of the long bones; shortened and tortuous femoral, tibia and fibula bones; enlarged femoral joints in the shape of the dumbbell; bilateral femur neck varus deformity; loose femoral head tissue; flattened knee joint epiphyseal; equinus and porous calcaneus (Fig. 2).
Metatropic dysplasia patient and her parents were sent for molecular genetic screening of mutations in the TRPV4 gene. We performed whole gene sequencing using primers flanking the open reading frame of the gene. It revealed a heterozygous non synonymous substitution c.245C>T (Fig. 3). At the protein level, the mutation leads to the amino acid substitution p.Pro82Leu in a very conservative position. This mutation was not previously reported, and was not detected in neither of the patient’s parents. The predicted functional effect of the missense variant was determined by PolyPhen as probably damaging with a score of 0.989. Also the mutation c.245C>T was not detected among 100 chromosomes in 50 healthy Circassians.

Conclusions. Here we describe the first case of MTD in Russia with confirmed by molecular genetic methods diagnosis. A novel de novo heterozygous missense mutation c.245C>T in TRPV4 gene has been revealed. These findings exclude autosomal recessive inheritance, and support the hypothesis of an autosomal dominant inheritance of MTD in the reported case with defined de novo missense mutation c.245C>T in TRPV4 gene. According to OMIM the probability of re-birth of the sick child in families with MTD is 1:20 because of gonadal mosaicism. So gonadal mosaicism should be suspected in each case de novo mutations in the TRPV4 gene. For the prevention of re-birth of children with MTD prenatal diagnosis in the next possible pregnancies in such families is recommended.

References
Plasma levels of IgG autoantibodies to the NMDA-receptors, human S-100 protein, and dopamine Type 2 receptors were detected in 26 males suffering from schizophrenia. Half of the patients had their levels of autoantibodies to the NMDA-receptors above average values, while in the rest of the group the antibody level was within norm. Following that, the patients were divided into two groups: Group 1 with a higher level of antibodies to the NMDA-receptors, Group 2 – with their normal levels of antibodies to the NMDA-receptor. The patients in the Group 1 also revealed significantly elevated levels of autoantibodies to the dopamine Type 2 receptors as well as to the S-100 protein in their blood plasma. Psychometric testing involving the PANSS scale showed that the positive symptoms’ values in the Group 1 were below those in the Group 2 while the negative symptoms’ values in the Group 1 were higher. Respectively, the composite index, which is determined as the difference between the positive and the negative scores, was lower in the Group 1 and higher in the Group 2.

Key words: schizophrenia, autoantibodies, NMDA-receptors, dopamine receptors, S-100 protein

Определяли содержание в плазме крови IgG аутоантител к NMDA-рецепторам, к белку S-100 человека и к дофаминовым рецепторам 2 типа у 26 мужчин, больных шизофренией. Уровень аутоантител к NMDA-рецепторам был выше нормальных значений у половины больных, у остальных – содержание антител было