doi: 10.21823/2311-2905-2020-26-3-141-149

Clinical and Radiological Characteristics of Two Patients with Acromesomelic Dysplasia Maroteaux Type with New Mutation in the *NRP2* Gene: Case Report

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Abstract

Background. Acromezomelic dysplasia Maroteaux type (AMDM) is a rare variant of autosomal recessive skeletal disorder. The disease is caused by mutations in the *NPR2* gene, coding the protein product which is one of the main regulators of endochondral ossification. To date, 49 mutations in this gene have been identified, more than half of which are missense substitutions. The presence of polymorphism of phenotypic manifestations makes it necessary to describe the features of clinical and radiological characteristics of the disease in patients with newly identified mutations in the gene, which will help to optimize its diagnosis. ***Case presentation.*** The clinical and radiological characteristics of two siblings with newly identified mutations c.125_126insTGGCG (p.Trp42CysfsTer12) and (p.Arg767Ter) in the *NPR2* gene are described. Intra-family polymorphism of clinical manifestations is shown. ***Discussion.*** Clinical manifestations and radiological data in two siblings with AMDM caused by new mutations in the *NPR2* gene and analysis of the literature data allowed us to conclude that there is no correlation of the severity of clinical signs and the type of mutations in the gene. Patients are born with normal growth and weight, and clinical manifestations (disproportionate dwarfism) appeared during the first year of life. The main radiological signs are shortening of tubular bones, most pronounced in the upper limbs and wedge-shaped formation of the vertebral bodies. Genotype-phenotype correlations confirmed the hypothesis that the majority of mutations leading to the disease is localized within the ligand-binding and guanylate cyclase domains. ***Conclusion.*** The obvious genetic heterogeneity, the similarity of the clinical manifestations of individual nosological groups of skeletal dysplasias, as well as the presence of intrafamily and interfamily polymorphism of clinical manifestations allows us to consider sequencing of a clinical exome or whole exome as the optimal method for diagnosing this group of diseases.

Keywords: acromezomelic dysplasia, *NPR2* gene, exome sequencing, case report.

Cite as: Markova T.V., Kenis V.M., Mironovich O.L., Shchagina O.A., Nagornova T.S., Melchenko E.V., Dadali E.L. [Clinical and Radiological Characteristics of Two Patients with Acromesomelic Dysplasia Maroteaux Type with New Mutation in the *NRP2* Gene]. *Travmatologiya i ortopediya Rossii* [Traumatology and Orthopedics of Russia]. 2020;26(3):141-149. (In Russian). doi: 10.21823/2311-2905-2020-26-3-141-149.

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Received: 21.05.2020. Accepted for publication: 19.06.2020.

Acromezomelic dysplasia, type Maroteaux (AMDM), OMIM:602875, is a rare autosomal recessive skeletal dysplasia with established prevalence 1: 1,000,000 [1]. The disease was first described by P. Maroteaux et al. in 1971 in the patients with dwarfism with a combination of mesomelic and acromelic shortening of the limbs, which the authors proposed to designate as "acromezomelic dwarfism" [2].

The main clinical manifestations of AMDM include disproportionate dwarfism, shortening of the limbs, mainly due to a decrease in the length of the forearms, legs and hands. In most of the described cases, there were no intellectual deficit and disorders of other organs and systems [1, 2, 3, 4, 5, 6, 7, 8]. On X-ray examination, in typical cases, shortening and deformation of long bones with hypoplasia of the distal ulna, subluxation/dislocation of the radial head, as well as wedge-shaped deformity of the vertebrae, shortening and expansion of the metacarpal bones and phalanges of the fingers are noted [9, 10, 11]. The first signs of the disease in some cases are noted from birth, these include a moderate shortening of long bones, however X-ray examination of newborns usually does not reveal deformities of bones or abnormalities of growth plates [1]. The distinct clinical and radiological signs of AMDM appear during the 1st or the 2nd year of life.

The disease is caused by mutations in the NPR2 gene located on chromosome 9p13 [12]. The gene is coding the protein functioning as a receptor for natriuretic peptide C, which plays a key role in the process of enchondral ossification. This protein regulates longitudinal bone growth expressing itself in the proliferative and hypertrophic zones of the growth plate chondrocytes. The pathogenesis of the disease has not been fully understood. It is believed that the disruption of this protein binding to its ligand leads to a change in the function of guanylate cyclase. The latter is involved in the formation of cyclic guanosine monophosphate (cGMP). The decreased concentration of cGMP causes the impairment of protein kinase activation and the interaction of signaling metabolic pathways of the growth plate resulted in the disturbance of chondrocytes proliferation and differentiation [13, 14, 15, 16]. 49 different mutations in the NPR2 gene (homozygous and compound-heterozygous) have been identified in the patients with AMDM from different populations, and the features of their clinical manifestations have been studied [16]. However, to date, there are no clear data on the features of clinical manifestations in the patients with different types and localization of mutations. This necessitates the description of genotype-phenotype correlations in the patients with newly identified mutations in the NPR2 gene.

The purpose of this study was to present the first description of the clinical and genetic characteristics of two Russian AMDM siblings with pronounced musculoskeletal involvement caused by newly identified mutations in the NPR2 gene.

Case presentation

Diagnosis

To clarify the patients' diagnosis, a complex of examination methods was used: genealogical analysis, clinical examination, neurological examination according to the standard technique with an assessment of the psychoemotional sphere, X-ray, and a new generation sequencing of clinical exome.

Isolation of genomic DNA was carried out from peripheral blood leukocytes using the Wizard Genomic DNA Purification Kit (Promega, USA) according to the manufacturer's protocol. The DNA concentration was measured after ultrasonic treatment, libraries and the final pool on a Qubit 2.0 device using reagents (qubit BR, qubit HS) from the manufacturer according to the standard protocol. The representation of DNA fragments of various lengths after ultrasonic treatment,

libraries, and the final pool was examined on a TapeStation 4200 using manufacturer's reagents (high sensitivity D1000) according to the standard protocol. The method of selective capture of DNA regions belonging to the coding regions of about 20,000 genes (IlluminaTruSeq® ExomeKit and IDT xGen® Exome Research Panel) was used for sample preparation. The average coverage of the patient's complete exome was × 98.5; the number of targeted areas with coverage ≥ × 10 – 93.16%; uniformity of coverage (uniformity Pct > 0.2 * mean) – 83.4%. To indicate the revealed variants, the nomenclature presented on the website http://varnomen.hgvs.org/recommendations/DNA, version 2.15.11 was used. The sequencing data were processed using the standard automated algorithm offered by Illumina for data analysis, available at https://basespace.illumina.com.

To assess the population frequencies of the identified variants, we used a sample of the 1000 Genome projects, ESP6500, and The Genome Aggregation Database v2.1.1. To assess the clinical relevance of the identified variants, the OMIM database, the HGMD® Professional pathogenic variants database version 2019.4 were used. Assessment of the pathogenicity and causality of genetic variants was carried out in accordance with international recommendations for the interpretation of the data obtained by massive parallel sequencing [17].

Validation genotyping of the identified variants in the proband, sibling and parents was carried out by direct automatic sequencing by Sanger according to the manufacturer's protocol on the ABI PRISM 3100 Genetic Analyzer (Applied Biosystems). The primer sequences were selected according to the reference sequence of the target regions of the NM_003995.3 (NPR2) gene.

The results of the patients' clinical and genetic analysis

The clinical, X-ray and molecular genetic examination of two siblings (boy and girl) was carried out. Their parents complained of short stature and disproportionate constitution of the boy aged 1 year and 10 months and the girl aged 1 year.

The siblings' parents are Tuvans by nationality. Both of them were healthy and not consanguineous. The age of both parents was 23 years. The mother's height was 151 cm, the father's – 168 cm. The first pregnancy in the family ended in spontaneous miscarriage at 3–4 weeks.

Patient 1 was a boy, born from the 2nd pregnancy and the first term birth. At the 33rd week of the pregnancy the ultrasound examination of the fetus revealed a shortening of the tubular bones. His birth weight was 3723 g, length – 50 cm, head circumference – 35 cm, chest – 34 cm. The Apgar score was 7/8 points. At birth, the signs of intrauterine hypoxia and right parietal cephalohematoma were revealed.

The early psychomotor development of the child proceeded according to his age. He began to rise his head from 2 months, sit from 6 months, walk from 1 year, speak single words at 1 year and 2 months. But there was a pronounced growth retardation. Due to the suspicion of skeletal dysplasia at the age of 1.5 years, an X-ray examination was carried out, which found the shortening and thickening of long and short tubular bones.

On physical examining a child at the age of 1 year 10 months demonstrated the significant delay in growth (68 cm, –8.4 SD), body weight 9 kg, macrocephaly with forehead bossing, the sparse hair, acro- and mesomelic shortening of the limbs, mainly of the forearms, wide hands with ulnar deviation, the brachydactyly of the hands and feet. There was marked hypermobility of the wrist joints in combination with stiffness of the elbow joints, the thoracolumbar kyphosis, and moderate diffuse muscular hypotonia (Fig. 1).

Patient 2 was a girl (the younger sister of patient 1). She was born from the 3rd pregnancy, the 2nd vaginal delivery at 37 weeks. Her weight at birth was 3120 g, length – 47

cm, head circumference – 35 cm, chest – 31 cm, the Apgar score 6/7 points due to signs of brain hypoxia. Her early development proceeded with a delay in the rate of motor skills acquisition. She began to rise her head at 6 months, turn over – at 7 months. She did not sit down on her own, did not get up, and uttered a few simple words at the time of her physical examination. Her neurological examination revealed moderate diffuse muscle hypotonia and tendon hyporeflexia. X-rays revealed changes in the long and short tubular bones similar to those of her brother, and a decrease in the anteroposterior size of the L2 vertebral body.

At her physical examination at the age of 1 year, her height was 54 cm (–10.9 SD), her body weight – 6 kg and head circumference – 44.5 cm. She had a large head, dolichocephalic in shape, with a prominent forehead (Fig. 2 a) and sparse hair. In the sitting position, the local lumbar kyphosis was noted (Fig. 2b). Also, there were found the shortening of the limbs, additional transverse skin folds of the forearms, broad short hands with brachydactyly, ulnar deviation of the hands, pronounced hypermobility in the joints of the hands, incomplete extension in the elbow joints, and hypotension of the abdominal muscles.

The both patients's spine X-rays showed a characteristic combination of the posterior wedge shape of the lower thoracic vertebrae, the anterior wedge shape of the upper lumbar vertebrae, and kyphosis in the lumbar spine (Fig. 3 a, b). The sister's spine X-ray changes were more pronounced and included impaired ossification of the anterior vertebral bodies in the form of lingual protrusions and L2 laterolisthesis (Fig. 3 c, d). The both siblings demonstrated the absence of the interpedicle distance widening in the lumbar spine. The chest X-rays showed curved and high clavicles (Fig. 3 b, d).

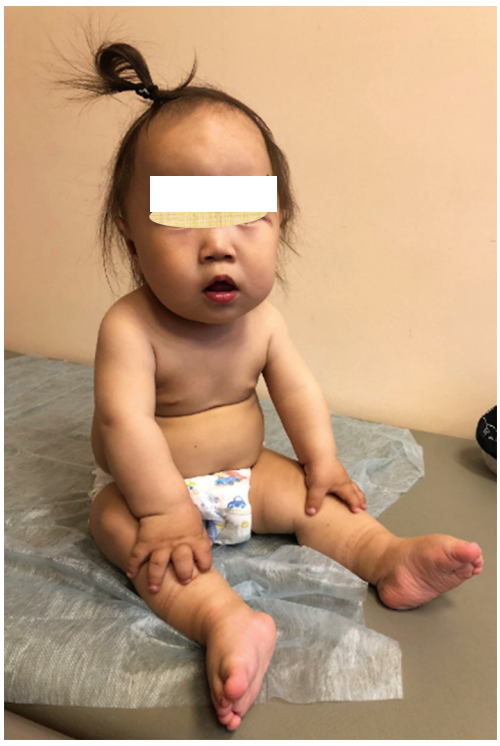

Figure 1. Patient 1, boy, 1 year 10 months.
Macrocephaly, shortening of the limbs, ulnar deviation of the hands, brachidactyly.

Figure 2. Patient 2, girl, 1 year old:
a — macrocephaly, short stature with shortened limbs, mainly the forearms, brachidactyly;
b — local lumbar kyphosis.

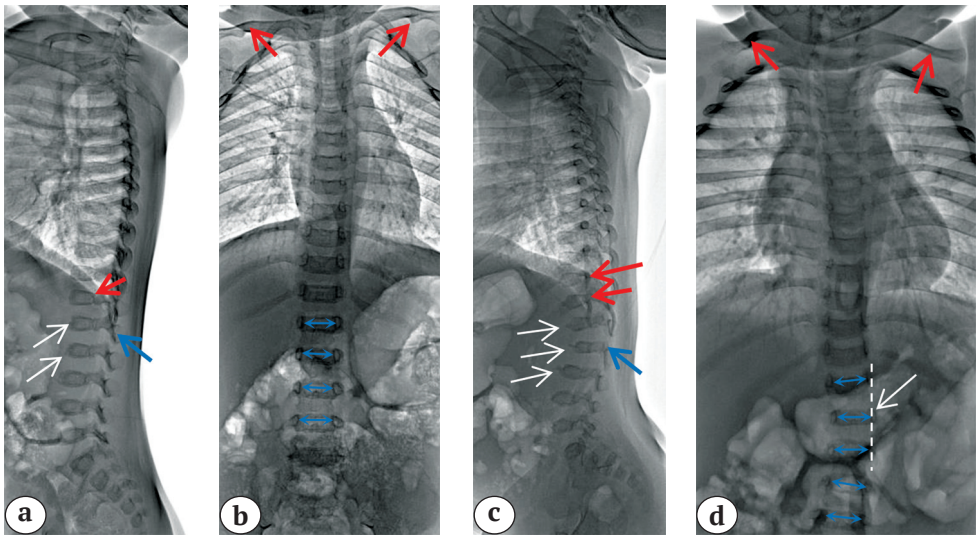

Figure 3. X-rays of the spine and chest of the patients 1 (a, b) and 2 (c, d): posterior wedging of lower thoracic vertebrae (a, c — red arrows); anterior wedging of upper lumbar vertebrae (a, c — white arrows); lumbar kyphosis (a, c — blue arrows); curved and high-positionrd clavicles (b, d — red arrows); the absence of an increase in the interpedicular distance in the lumbar spine (b, d — blue arrows); laterolisthesis L2 (d — white arrow).

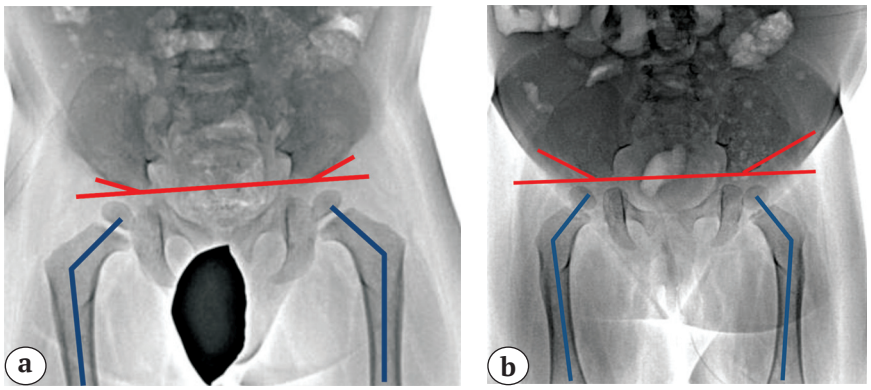

Figure 4. X-rays of the hip joints of patients 1 (a) and 2 (b): increased acetabular index (red lines) and neck-shaft angle (blue lines).

The hip joints X-rays showed moderate signs of dysplasia (an increase in the acetabular index and neck-shaft angle), which did not require orthopedic treatment (Fig. 4).

The forearms and hands X-rays showed shortening and deformity of the ulna, dorsal subluxation of the radial head, ulnar deviation of the hands, shortening and widening of the proximal and middle phalanges of the fingers (Fig. 5).

The skull X-ray revealed an elongated sella turcica, the presence of Wormian bones and dolichocephaly (Fig. 6).

The genealogical analysis, specific clinical symptoms and X-ray changes suggested the presence of a rare autosomal recessive skeletal dysplasia variant. The diagnosis of AMDM was established by exome sequencing which revealed 2 variants of the NPR2 gene, not previously described as pathogenic: the insertion of 5 nucleotides in the first exon (chr9: 35792530G> GTGGCG, c.125_126insTGGCG). This insertion resulted in the frame shift and stop codon formation (p.Trp42CysfsTer12, NM_003995.3) and single nucleotide substitution (p.Arg767Ter, NM_003995.3) in exon 15 (chr9: 35806157C> T, c.2299C> T). These followed by the formation of a premature stop codon (p.Arg767Ter, NM_003995.3). Both variants were identified in the proband in a homozygous state.

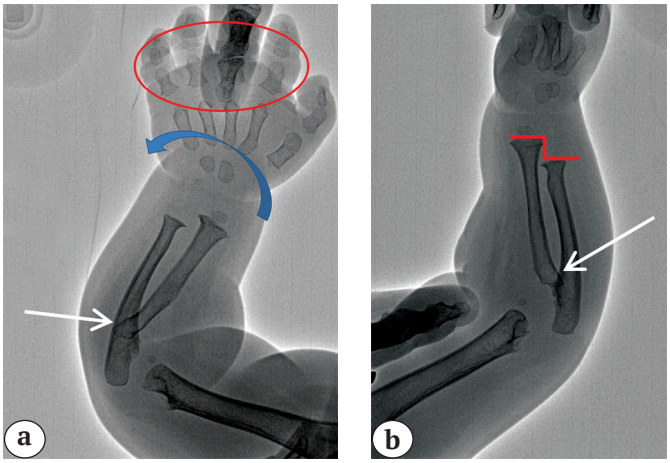

Figure 5. X-rays of the forearm and hand of patient 2 (a — anteroposerior, b — lateral view): relative shortening of the ulna (red line); dorsal subluxation of the radial head (white arrows); ulnar deviation of the hand (blue arrow); short and wide basal and middle phalanges of the fingers (red circle).

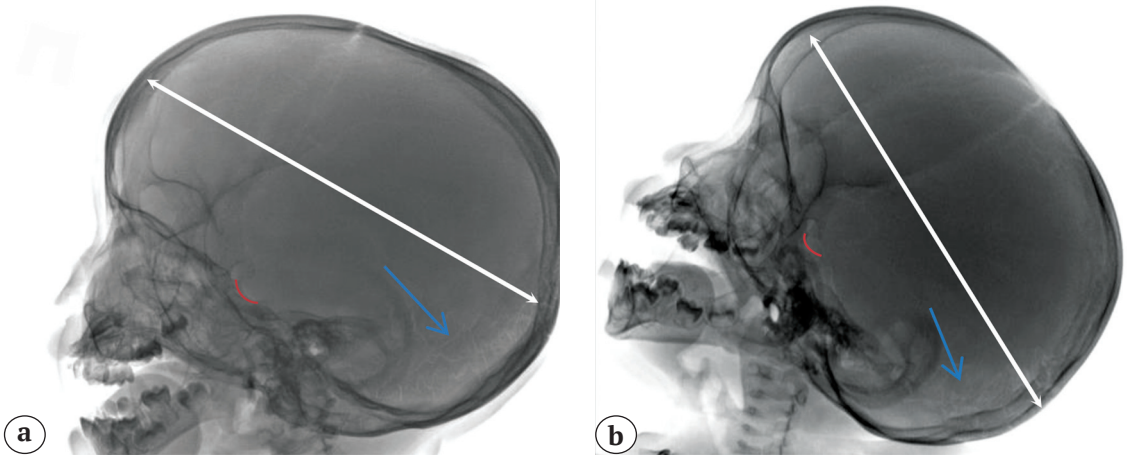

Figure 6. Lateral X-rays of the skull of patients 1 (a) and 2 (b): dolichocephaly (white arrows): an elongated sella turcica (red lines); vermian bones (blue arrows).

As in the majority of the AMDM patients described in the literature, in our cases, the mutations were localized in the exons of the gene encoding the amino acid sequences of the ligand-binding and guanylate cyclase protein domains, which indicates their important function in the process of bone formation (Fig. 7).

Discussion

AMDM is one of the genetic variants of isolated acromezomelic dysplasias with an autosomal recessive inheritance. To date, 3 genetic variants of this group of diseases were described. In addition to AMDM, the Grebe (OMIM: 200700) and Hunter-Thomsen (OMIM: 201250) types are distinguished,

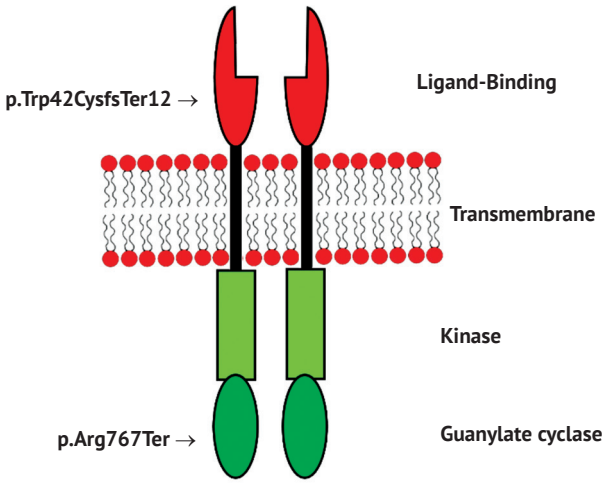

Figure 7. Localization of amino-acid substitutions in the domains of the NPR2 protein in siblings with AMDM.

which are allelic variants due to mutations in the GDF5 gene. Unlike AMDM, the clinical manifestations of the other two acromezomelic dysplasia variants are characterized by more severe clinical signs with predominant lesion of the lower extremities, a pronounced decrease in the size and curvature of the long bones, hypoplasia or aplasia of the metacarpal and metatarsal bones, as well as proximal and distal phalanges of the fingers and toes [3].

We described the clinical and X-ray characteristics of two siblings with newly identified mutations in the NPR2 gene. The family lived in the Republic of Tuva, located in the south of Eastern Siberia with a population of 327,388 people. The parents denied the existence of consanguinity and belonged to different ethnic groups of Tuvans. The clinical manifestation of the disease in both siblings was typical for AMDM and characterized by disproportionate dwarfism, shortening of the middle and distal segments of the limbs, mainly the upper ones. Like most patients described in the literature, the siblings, we observed, were born with normal height and weight parameters. The clinical manifestation like growth retardation and limb shortening and X-ray signs of the disease became obvious in the 1st year of their life.

The spine X-rays revealed the ossification delay of the vertebrae with their secondary deformity (posterior wedge shape of the lower thoracic vertebrae and the anterior wedge shape of the upper lumbar vertebrae, lumbar kyphosis, and the absence of an increase in the interpedicle distances in the lumbar spine. X-rays of the extremities revealed shortening of the ulna, dorsal subluxation of the radial head and deformity of the diaphysis, shortening and widening of the phalanges of the fingers. Both siblings had macrocephaly and moderate diffuse muscular hypotonia. Intellectual development and speech of the both patients was according to their age. It should be noted that the general clinical manifestation in the sister was more pronounced and characterized by a significant delay in growth (–10.9 SD) and the motor development, as well as deformation of the radius, shortening and widening of the tubular bones to a significant extent. Additional signs in these siblings were limited extension in the elbow joints, ulnar deviation of the hands, as well as dolichocephaly, elongation of the sella turcica, and the presence of Wormian bones on the skull X-ray. Some differences in the severity of clinical manifestation in affected siblings were also noted. The youngest child, in addition to the pronounced typical signs of AMDM demonstrated a delay in the early motor development, but the presence of these symptoms may be due to hypoxic brain injury in the perinatal period.

Clinical sequencing of the exome revealed two previously undescribed mutations in the NPR2 gene: the insertion of 5 nucleotides c.125_126insTGGCG (p.Trp42CysfsTer12) in exon 1 and the single nucleotide substitution c.2299C> T (p.Arg767Ter) in exon 15. Both mutations led to the formation of a stop-codon.

Both variants identified in the patients are pathogenic according to the ACMG criteria. However, the insertion c.125_126insTGGCG is located in exon 1 and leads to the termination of the protein product translation of the gene through 12 amino acid residues; therefore, it is obvious that the p.Arg767Ter variant in exon 15 cannot affect the phenotype, but is simply included in the complex allele. Thus, the molecular cause of AMDM in the described family is the pathogenic variant c.125_126insTGGCG (p.Trp42CysfsTer12) in a homozygous state.

It is known that the NPR2 gene contains 22 exons and encodes a homodimeric protein consisting of 4 domains: ligand-binding, transmembrane, protein kinase, and guanylate cyclase [18]. To date, 49 mutations in the NPR2 gene have been described, leading to the AMDM development. The majority of mutations (57.1%) are missense substitutions.

Only 4 mutations of the splice site (8.2%), 9 nonsense mutations (18.4%), and 8 (16.3%) mutations with a shift in the reading frame were identified, 7 of which are represented by deletions not divisible by three nucleotides, and only one mutation identified by CF Bartels et al. in 2004 in a Lebanese patient is an insertion in combination with the deletion of c.2304_2307delTTGGinsCTGATGGA (p.Trp769*) [1]. Thus, the discovered insertion of five nucleotides in exon 15 of the gene is the 2nd case of AMDM caused by this type of mutation.

As in the majority of AMDM patients described in the literature, in the patients we observed, the mutations were localized in the exons of the gene encoding the amino acid sequences of the ligand-binding and guanylate cyclase protein domains, which indicates their important function in the process of bone formation (Fig. 7). The results of clinical and genetic examination of the patients allowed us to obtain one more evidence in favor of the fact that mutations in the regions of the NPR2 gene encoding the amino acid sequence of the ligand-binding and guanylate cyclase domains lead to this nosological form.

In recent years, due to achievements of molecular genetic testing, it was possible to clarify the etiopathogenetic mechanisms of a large number of monogenic variants of skeletal dysplasias. Identification of mutations responsible for the certain genetic variant of this group of diseases development allows us to determine the range of its clinical manifestation and significantly increase the effectiveness of medical and genetic counseling for the families, aimed at preventing the occurrence of repeated cases of the disease in such families. The pronounced genetic heterogeneity of skeletal dysplasias sharing common features like short stature and deformities of the limbs and spine, as well as the significant size of the genes responsible for their occurrence, make it possible to recommend the use of clinical or whole exome sequencing as the main method for diagnosing in this group of diseases.

Consent

Written informed consent was obtained from the parents of the sick siblings to conduct the molecular genetic testing of the blood samples and permission to anonymously publish the study results.

Competing interests: The authors declare no conflict of interest.

Funding: The state budget.

Authors' contributions

T.V. Markova – collection and processing of clinical material, literature review, text preparation.

V.M. Kenis – research design, text editing.

O.L. Mironovich – laboratory molecular genetic diagnostics, data analysis, text preparation.

O.A. Shchagina – processing and analysis of the laboratory data, text editing.

T.S. Nagornova – laboratory molecular genetic diagnostics, data analysis, text preparation.

E.V. Melchenko – data analysis, text preparation.

E.L. Dadali – research concept, text editing.

All authors made a significant contribution to the research and preparation of the article and read and approved the final version before its publication. They agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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