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ULLRICH CONGENITAL MUSCULAR DYSTROPHY: CLINICAL CASE STUDY

Introduction. Ullrich congenital muscular dystrophy (Ullrich CMD, OMIM #254090) is the most severe form of skeletal muscle collagenopathy associated with three genes (*COL6A1, COL6A2, COL6A3*).

The purpose of the report was to present our own observation of clinical cases with Ullrich congenital muscular dystrophy in two unrelated Yakut families.

Materials and methods. A clinical and genealogical examination, electroneuromyography, muscle MRI, muscle biopsy, and molecular genetic research using the massively parallel sequencing method were carried out.

Results. The cause of the disease in the first family was two mutations in a compound heterozygous state: c.1561C>T and c.2329T>C in the *COL6A2* gene; in the second family, the c.2329T>C mutation in the *COL6A2* gene in a homozygous state. The clinical picture of the disease was manifested by muscle weakness and hypotonia, hypermobility of the interphalangeal joints, contractures of the elbow, ankle and knee joints, delayed motor development, spinal deformity, and skin changes. The type of inheritance in families is autosomal recessive.

Conclusions. Despite the rarity of the disease, neurologists and geneticists, when identifying symptoms of myopathy, delayed motor development, and the presence of hypermobility in the distal joints, contrasting with retractions of the proximal and axial joints, must be alert to Ullrich CMD. Next-generation sequencing techniques make it easier to diagnose the disease.

Keywords: congenital muscular dystrophy, Ullrich's disease, *COL6A2*, Yakut family, clinical case.

Introduction. Congenital Ullrich muscular dystrophy (Ullrich CMD, OMIM #254090) is the most severe form of collagenopathy. It was first described by Ullrich in 1930 and is associated with a deficiency of type VI collagen. Type VI collagen is a protein heterotrimer of the extracellular matrix, essential for the functioning of skeletal muscle and skin, present in the stroma of internal organs, and also forms a microfibrillar network closely associated with the basement membrane in most tissues of the body. It consists of three peptide chains, each of which is encoded by a separate gene: *COL6A1* and *COL6A2* (locus 21q22.3) and the *COL6A3* gene (locus 2q37). Mutations of these three genes lead to the development of myopathies - from the more severe form of Ullrich CMD to the milder in children form of Bethlem CMD in adults (OMIM 158810). The prevalence of Ullrich CMD is 0.13 per 100,000 population, Bethlem CMD is 0.5 per 100,000 population. In Russia there are isolated descriptions of clinical cases. The classic clinical picture includes muscle hypotonia and weakness, marked hypermobility in the distal joints, contrasting with retractions of the proximal and axial joints.

Materials and methods. Medical-genetic center of the State Autonomous Institution of the Republic of Sakha (Yakutia) Republican Hospital No. 1 - National Center of Medicine named after Nikolaev M.E. observed three patients from two unrelated yakut families with undifferentiated form of congenital muscular dystrophy. To diagnose these cases, clinical and genealogical examination, electroneuromyography (Neurosoft device, Ivanovo), and molecular genetic research using the massively parallel sequencing (MPS) method were carried out at the medical genetic center "Genotek" (Moscow). Validation of the results was carried out using the direct Sanger sequencing method on an automatic sequencer ABI 3500 (USA) in the research laboratory “Molecular medicine and human genetics” of the Medical Institute of the North-Eastern Federal University named after. M.K. Ammosova". The primer sequence is shown in Table 1.

The study was approved by the local committee on biomedical ethics of the NEFU named after. M.K. Ammosov" (Extract from protocol No. 22 dated February 26, 2020): carried out without violations of ethical and legal standards. All study participants signed voluntary consent.

Results and discussion. *Family 1*. Child S. born in 2009, boy, Yakut ethnic group. Only child. Parents deny consanguineous marriage. First case in the family.

From the medical history: a child from the first normal pregnancy, term birth. He screamed immediately, birth weight 2900 g, height 52 cm, Apgar score 8/9 points. Prolonged physiological jaundice was observed. Psychomotor development with delay: began to hold his head from 6 months, sit from 8-9 months, phrase speech from 2 years, intelligence was in accordance to the age, began to walk from 2 years, fell often, from 3 years he stopped walking independently. From 6 months annually underwent examination and treatment in the psychoneurological department and rehabilitation center with suspected neuromuscular disease due to the presence of signs of myodystrophy. In 2012, a child aged 3 years was sent to the Medical Genetic Center (MGC) of the State Autonomous Institution of the Republic of Sakha (Yakutia) Republican Hospital No. 1 - National Center of Medicine named after Nikolaev M.E. to clarify the diagnosis. At the time of examination, the child had severe muscle weakness, weight loss, and a myopathic “duck-like” gait. Can't run or jump. He holds his head satisfactorily in a sitting position, but cannot lift his head from a lying position. Sits steadily and stands up with support.

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Table 1

Sequence of primers for validation of mutations in the *COL6A2* gene using direct Sanger sequencing

Mutation	Forward (5′→ 3′)	Reverse (5′→ 3′)
c2329T>C (p.Cys777Arg)	GCG-GTG-GTC-ATC-ACG-GAC	ATC-CTG-GGC-TGC-ACA-TTC-ATC
c.1561C>T (p.Arg521Ter)	CTC-TGC-TCA-CAG-CCA-GAAC	GAC-CTA-TCC-TTC-ACT-GAG-TC

The shape of the head is hydrocephalic, high forehead, pronounced vascular pattern on the forehead. Laboratory and instrumental diagnostics were carried out. General and biochemical blood tests were without abnormalities. The level of creatinine phosphokinase is normal. A molecular genetic study did not detect deletions of exons 7 and 8 of the SMN1 gene.

In March 2014 (at 5 years old), the patient was hospitalized in the second department of psychoneurology of the Research Institute of Pediatrics and Pediatric Surgery (Moscow, Russia) in order to clarify the diagnosis. The results of laboratory and instrumental studies: general and biochemical blood tests were unchanged. According to electrocardiography (ECG), migration of the supraventricular pacemaker was recorded against the background of minor tachycardia, moderate arrhythmia, incomplete blockade of the right bundle branch, increased electrical activity of the right ventricle, and disruption of the repolarization process in the myocardium of the posterior wall of the left ventricle. Muscle MRI was performed: severe diffuse damage to the thigh muscles with the presence of a "tiger stripe" effect in the anterior group; pronounced diffuse damage to the muscles of the leg with the greatest interest in the posterior group. MRI conclusion: the MRI pattern may be consistent with collagenopathy. Based on clinical history and instrumental studies, the patient was given a clinical diagnosis of congenital muscular dystrophy, collagenopathy.

In 2017 (at 8 years), upon examination of the patient, generalized muscle weakness, wasting of all muscles, contractures of the elbow, knee, and ankle joints were revealed, contrasting with distal hypermobility; hyperkeratosis was noted on the skin. Full exome sequencing was carried out: two previously described mutations in the compound heterozygous state were identified in the *COL6A2* gene on chromosome 21: c.1561C>T (p.Arg521Ter) in exon 19 (rs773686174) and c.2329T>C (p.Cys777Arg) in exon 26 exon (rs267606747) [7, 8]. Validation of the results of exome sequencing con-

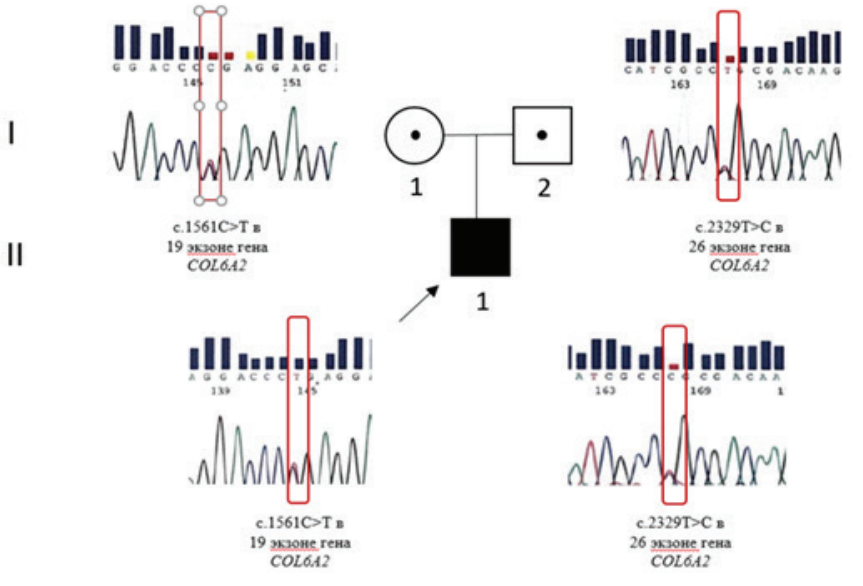

Fig. 1. A fragment of the family tree 1 is presented with the results of Sanger sequencing. I-1 mother of the proband: healthy, heterozygous carrier of the c.1561C>T mutation in exon 19 of the *COL6A2* gene; I-2 father of the proband (marked by arrow): healthy, heterozygous carrier of the c.2329T>C mutation in exon 26 of the *COL6A2* gene; II-1 proband: patient with Ullrich CMD, two mutations were found in the compound heterozygous state: c.1561C>T in exon 19 and c.2329T>C in exon 26 of the *COL6A2* gene.

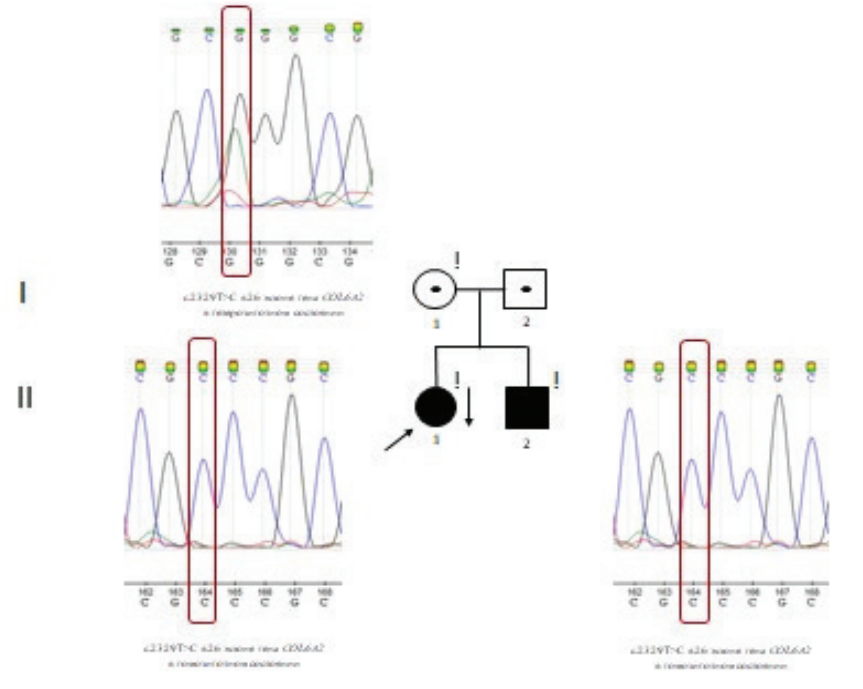

Fig. 2. The pedigree of the family 2 is presented. II-1 – proband (marked by arrow), patient with Ulrich CMD; II-2 sibling of the proband, patient with Ulrich CMD; I-1 mother of the proband, healthy, heterozygous carrier of the c.2329T>C mutation in exon 26 of the *COL6A2* gene; I-2 the proband's father is healthy (not examined), a heterozygous carrier of the mutation is assumed.

firmed the presence of a mutation in the proband; the mother was diagnosed with the c.1561C>T mutation in exon 19 of the *COL6A2* gene in a heterozygous state; the father has the c.2329T>C mutation in exon 26 of the *COL6A2* gene, also in a heterozygous state (Fig. 1). Thus, based on clinical and anamnestic data and molecular genetic analysis, the patient was given a final diagnosis of Ullrich congenital myodystrophy (OMIM #254090).

Family 2. Proband E. born in 2007, girl, Yakut ethnic group. She was observed at the medical genetic center from an early age for floppy child syndrome. The family pedigree is shown in Fig. 2.

A child from the first pregnancy, which occurred in the second half on the background of exacerbation of chronic pyelonephritis. Body weight at birth was 2880 g, height 50 cm. She screamed immediately. Psychomotor development with delay. At 7 months of age, she was consulted by a geneticist regarding floppy baby syndrome. Direct DNA diagnostics of Werdnig-Hoffmann spinal amyotrophy was carried out: no deletion of exons 7 and 8 of the SMN1 gene was detected. Repeated consultation at the age of 1 year 10 months, there were complaints of drooling and weakness. At the age of 4 years, an examination in the neuropsychiatric department revealed elevated LDH and CPK results, she was consulted by a neurogeneticist, and signs of myodystrophy were identified. The progression of the disease was noted in the form of an increase in muscle weakness, she could not sit or run on her own, she began to often stumble and fall, she stopped climbing stairs on her own, and there was a decrease in body weight. Needle EMG was not performed for technical reasons. According to stimulation electroneuromyography, a decrease in motor responses was detected.

In 2012, at 5 years old she was at the Federal State Budgetary Institution Moscow Research Institute of Pediatrics and Pediatric Surgery in the Department of Psychoneurology and Epileptology No. 1 with a diagnosis of Bethlem congenital muscular dystrophy. An MRI of the muscles was performed - a study of the muscles of the thigh and lower leg revealed dystrophic changes in the muscle's characteristic of collagenopathy. The results of a muscle biopsy revealed signs of muscular dystrophy; immunohistochemical analysis revealed the absence of collagen.

In 2018, at 11 years old, the girl was again consulted by a geneticist. At the age of 10 years, the progression of the disease was noted - she stopped

Table 2

Clinical and genetic characteristics of patients

Family	Patient	Gene, mutation	Gender	Age at which independent walking begins	Contractures	Changes in the skin	Spinal deformity	Echo-KG	CPK level (norm 38-174 U/l), LDH (norm 0-247 U/l)
I	S	*COL6A2*, c.2329T>C and c.1561C>T in compound heterozygous state	male	started walking at the age of 2	yes	hyperkeratosis	yes	Congenital heart defect: VSD	Normal CPK / Normal LDH
II	P	*COL6A2*, c.2329T>C in homozygous state	male	started walking at the age of 1 year 3 months	yes	keloid scar at the site of wound healing after muscle biopsy	yes	Signs of cardiomyopathy	CPK level is normal, LDH is increased: 253.6 U/l
	E	*COL6A2*, c.2329T>C in homozygous state	female	started walking at the age of 1 year 2 months	yes	"goose bumps", focal rounded hypertrichosis on the back, keloid scar at the site of wound healing after muscle biopsy	Yes	AV insufficiency grade 1-2. Front wall seal MV. Slight expansion of the aircraft trunk. Additional trabecula in the LV cavity	CPK level increased: 232 U/l / Normal LDH

VSD – ventricular septal defect; AV – aortic valve; MV – mitral valve; PA – pulmonary artery; CPK – creatinine phosphokinase; LDH – lactate dehydrogenase; AR – autosomal recessive type of inheritance, LV - left ventricle

walking and standing, kyphoscoliosis worsened, she began to eat and dress with outside help, and a tendency to constipation appeared. The physique is asthenic. Moves in a wheelchair. The skin is dark, «goose pimples», focal rounded hypertrichosis on the back, a keloid scar at the site of wound healing after muscle biopsy. Subcutaneous fatty tissue is underdeveloped. Severe hypotrophy of all muscle groups. Contracture of the elbow, knee, ankle joints, hypermobility of the interphalangeal joints. The face is symmetrical, no microanomalies of development were identified. The torso is proportional, the chest is deformed and flat. Severe kyphoscoliosis, flat back, "wing-shaped" shoulder blades. Neurological status: there are no abnormalities in the cranial nerves. Moderate tetraparesis. Muscle tone in the limbs is low. Hypotrophy of all muscles. Tendon reflexes from the limbs are low, D=S. There are no pathological or meningeal signs. Sensitivity is not impaired. Coordinator tests are performed satisfactorily. There are no pathological signs. Contractures of the wrist, ankle, knee, elbow joints. He can't walk on his own, he can't stand it. Speech is normal.

Results of instrumental studies. An X-ray of the thoracic spine revealed right-sided thoracolumbar kyphoscoliosis of the 2nd degree, an anomaly of the lumbosacral spine. According to the ECG, it is a variant of the age norm. According to spirometry, there is a severe disorder of the restrictive type. Obstructive type disorder of moderate severity. The patient is unable to perform forced breathing maneuvers. The child underwent molecular genetic diagnostics using the MPS method using Clinical Exome kits (Illumina Inc., USA). As a result of exome sequencing, the previously described mutation c.2329T>C (p.Cys777Arg) in exon 26 of the *COL6A2* gene was identified in a homozygous state (rs267606747), the same mutation was found in the mother in a heterozygous state, the father of the patients from DNA diagnostics refused (Fig. 2). The patient died suddenly at home from respiratory problems in 2018 at the age of 11 years.

Patient P., born in 2011, boy, Yakut ethnic group, sibling of proband E. From the anamnesis: a child from the second pregnancy, which proceeded well. Second birth, urgent. He screamed right away. Body weight at birth 4100 g, length 56 cm, Apgar 7/8 b. Early development with delay: holds head from 3 months, sits from 11 months, walks from 1 year 3 months. At 1 year 1 month. There were complaints about the lack of independent walking.

The phenotype is generally similar to his sister. The physique is asthenic. On the skin side - a keloid scar at the site of wound healing after taking a biopsy. Neurological status: no features from the cranial nerves. Moderate tetraparesis. Muscle tone in the limbs is low. Severe hypotrophy of all muscle groups. Tendon reflexes from the limbs are low, D=S. Contractures of the elbow, knee, ankle joints, hypermobility of the interphalangeal joints. Frequent falls. The gait is changed, he walks on tiptoes with support slowly. A laboratory and instrumental examination were carried out. X-ray of the thoracic spine in 2017 revealed a slightly pronounced kyphotic deformity of the thoracic spine. Needle EMG was not performed for technical reasons. Spirometry from 2018: severe ventilation impairment of mixed type. The cause was the same mutation as sister's one.

Table 2 presents the clinical and genetic characteristics of our patients with congenital Ullrich myodystrophy. When comparing probands from the two presented unrelated Yakut families, it can be noted that in a patient from the first family with a mutation in the compound heterozygous state, muscle weakness was more pronounced, the onset of walking was later than in patients from the second family, from the age of two; however, the levels of CPK and LDH were normal. In general, the clinical manifestations of the disease in our patients are the same as those described in the literature and reflect lesions associated with collagen VI deficiency.

Conclusion. Thus, in the presented families, the cause of the disease was mutations in the *COL6A2* gene of chromosome 21. In the first family, the cause was two mutations in the compound heterozygous state (c.1561C>T и c.2329T>C), and in the second family, mutation c.2329T >C in the homozygous state. Despite the rarity of Ulrich's CMD, neurologists and geneticists need to be alert to this pathology.

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