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Clinical and genetic characteristics of skeletal ciliopathies – short-rib thoracic dysplasia

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BACKGROUND: Ciliopathies include the large group of hereditary diseases caused by mutations in the genes encoding primary cilia components. The largest type of skeletal ciliopathies is short-rib thoracic dysplasia.

AIM: This study describes the clinical and genetic characteristics of Russian patients with STRD with or without polydactyly caused by mutations in the genes *DYNC2H1*, *DYNC2I2*, *IFT80*, and *IFT140*.

MATERIALS AND METHODS: A comprehensive examination of 10 unrelated children aged from 9 days to 9 years, with phenotypic signs of short-rib thoracic dysplasia with or without polydactyly, was conducted. The diagnosis was confirmed using genealogical analysis, clinical examination, neurological examination, radiography, and targeted sequencing of a panel consisting of 166 genes responsible for the development of inherited skeletal pathology.

RESULTS: As a result of the molecular genetic analysis, four short-rib thoracic dysplasia genetic variants were identified. Seven patients were diagnosed with short-rib thoracic dysplasia type 3, and three unique patients were diagnosed with types 11, 2, and 9 due to mutations in the *DYNC2H1* and *DYNC2I2*, *IFT80*, and *IFT140* genes, respectively. From the 14 detected variants, six were identified for the first time. As in the previously described patient samples, in the analyzed sample, more than half of the cases were due to a mutation in the *DYNC2H1* gene, which is responsible for the SRTD type 3. The differences in the severity of clinical manifestations and the disease course in patients with mutations in certain regions of the gene, which have a different effect on its protein product function, have been shown.

CONCLUSIONS: The results of this molecular genetic study broaden the spectrum of mutations in the *DYNC2H1*, *DYNC2I2*, and *IFT140* genes causing short-rib thoracic dysplasia and confirm the usefulness of the whole-exome sequencing as the most informative method for identifying mutations of the genetically heterogeneous short-rib thoracic dysplasia group.

Keywords: skeletal ciliopathies; short-rib thoracic dysplasia; exome sequencing.

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Научная статья

Клинико-генетические характеристики скелетных цилиопатий — торакальных дисплазий с короткими ребрами

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Обоснование. Цилиопатии — большая группа наследственных заболеваний, обусловленных мутациями в генах, кодирующих различные компоненты первичных ресничек. Наиболее многочисленную группу скелетных цилиопатий составляют торакальные дисплазии с короткими ребрами.

Цель — описание клинико-генетических характеристик российских больных торакальными дисплазиями с короткими ребрами с или без полидактилии, обусловленными мутациями в генах *DYNC2H1*, *DYNC2I2*, *IFT80*, *IFT140*.

Материалы и методы. Проведено комплексное обследование 10 детей из неродственных семей в возрасте от 9 сут жизни до 9 лет с фенотипическими признаками торакальной дисплазии с короткими ребрами с или без полидактилии. Для уточнения диагноза использовали генеалогический анализ, клиническое обследование, неврологический осмотр по стандартной методике с оценкой психоэмоциональной сферы, рентгенографию и таргетное секвенирование панели, состоящей из 166 генов, ответственных за развитие наследственной скелетной патологии.

Результаты. В результате молекулярно-генетического анализа у наблюдаемых больных выявлено четыре генетических варианта торакальной дисплазии с короткими ребрами. У семерых больных диагностирована торакальная дисплазия с короткими ребрами 3-го типа, по одному больному — дисплазии 11, 2 и 9-го типа, обусловленные мутациями в генах *DYNC2H1*, *DYNC2I2*, *IFT80* и *IFT140* соответственно. Из 14 нуклеотидных замен шесть обнаружены впервые. Как и в ранее описанных выборках, у большинства анализируемых пациентов заболевание обусловлено мутацией в гене *DYNC2H1*, ответственном за возникновение торакальной дисплазии с короткими ребрами 3-го типа. Существуют различия в тяжести клинических проявлений и течении заболевания у больных с мутациями в отдельных участках гена, оказывающих различное влияние на функцию его белкового продукта.

Заключение. Результаты молекулярно-генетического исследования расширяют спектр мутаций в генах *DYNC2H1*, *DYNC2I2*, *IFT140*, обуславливающих развитие торакальной дисплазии с короткими ребрами 3, 11 и 9-го типов и подтверждают использование секвенирования экзома как основного метода идентификации мутаций генетически гетерогенной группы торакальных дисплазий с короткими ребрами.

Ключевые слова: скелетные цилиопатии; торакальные дисплазии с короткими ребрами; секвенирование экзома.

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BACKGROUND

Ciliopathies represent a large group of hereditary diseases caused by mutations in genes encoding various components of primary cilia, which are apical outgrowths of the basement membrane of cells containing microtubules [1, 2]. The main function of the cilia is to perceive various extracellular signals through surface receptors and transmit them to the cell nucleus. The cilia play a key role in the embryonic and post-natal development of various organs, including the formation of the skeleton, providing endochondral ossification [3, 4]. The classification of skeletal ciliopathies has been revised many times. Currently, three groups of skeletal ciliopathies can be distinguished, namely, short-rib thoracic dysplasia (SRTD) with or without polydactyly, Ellis–van Creveld syndrome, and Sensenbrenner’s cranioectodermal dysplasia. The most numerous group of skeletal ciliopathies is represented by SRTDs. They were first described by Jeune et al. in 1955, and for a long time, the disease was called asphyxial thoracic Jeune dystrophy [5]. However, to date, 20 genetic variants of SRTD with an autosomal recessive type of inheritance have been detected, and 19 genes responsible for their occurrence have been identified [6]. The protein products of these genes are mainly involved in the anterograde and retrograde transport of various substrates along cilia microtubules [2–4]. Typical clinical manifestations of SRTD are represented by a bell-shaped deformity of the chest, leading to respiratory disorders, and rhizomelic shortening of the limbs and brachydactyly. Some patients have polydactyly and damage to the kidneys, liver, eye, heart, and brain [2, 4, 7]. Significant mortality is due to cardiorespiratory failure that develops following chest constriction and progressive damage to the kidneys and liver [7]. In 20%–60% of patients with various genetic variants of SRTD, a lethal outcome is registered in the neonatal period [1]. The main radiological sign of the disease is chest hypoplasia caused by rib shortening and formation of the so-called trident in the region of the acetabulum of the ilium [8].

Specific clinical signs suggest SRTD on clinical examination. However, the variability of the clinical manifestations and severity of the disease course in genetic variants necessitate the study of their clinical aspects, which is important for predicting the severity of the disease course and planning the therapeutic and preventive measures.

The study aimed to analyze the clinical and genetic characteristics of Russian patients with SRTD with or without polydactyly, caused by *DYNC2H1*, *DYNC2I2*, *IFT80*, and *IFT140* mutations.

MATERIALS AND METHODS

A comprehensive examination of 10 children from unrelated families, aged 9 days to 9 years, with phenotypic signs of SRTD with or without polydactyly was conducted.

To clarify the diagnosis, we conducted genealogical analysis, clinical examination, and neurological examination according to the standard method with an assessment of the psycho-emotional sphere, radiography, and targeted sequencing of a panel consisting of 166 genes responsible for the development of hereditary skeletal pathology.

Genomic DNA was isolated from whole blood using the DNAEasy kit (QiaGen, Germany) according to the manufacturer’s standard protocol. The concentration of DNA and libraries was measured on a qubit2.0 device using reagents (qubit BR and qubit HS) following the manufacturer’s standard protocol. For sample preparation, a technique based on the multiplex polymerase chain reaction of target DNA regions was used. Next-generation sequencing was performed on an Ion Torrent S5 sequencer with an average coverage of at least $\times 80$ and number of target areas with coverage of 90%–94% or more. For the annotation of the identified variants, the nomenclature presented on <http://varnomen.hgvs.org/recommendations/DNA> (version 2.15.11) was used. Sequencing data were processed according to the Ion Torrent standard automated algorithm.

To assess the population frequencies of the identified variants, the samples of the 1000 Genomes, ESP6500, and Genome Aggregation Database v2.1.1 were used, and to assess the clinical significance, the OMIM database and the HGMD® Professional pathogenic variants database (version 2021.3) were used. The pathogenicity and causes of the genetic variants were analyzed in accordance with international recommendations for the interpretation of data obtained by massive parallel sequencing [9].

Validation of the variants identified in probands and genotyping of siblings and parents were performed by direct automatic Sanger sequencing in accordance with the manufacturer’s protocol on an ABIPrism 3500xl apparatus (Applied Biosystems). Primer sequences were selected according to the reference sequence of the target gene regions *DYNC2H1* (NM_001080463), *DYNC2I2* (*WDR34*) (NM_052844), *IFT80* (NM_020800), and *IFT140* (NM_014714).

RESULTS

Ten unrelated patients (5 boys and 5 girls) with clinical and radiological manifestations of SRTD with or without polydactyly were followed up. Two of the children had parents who were related by blood. In two more families, the anamnesis was aggravated by the death of the older child in the neonatal period and at age 10 months with clinical manifestations similar to those of the probands. In three families, the obstetric anamnesis was remarkable for spontaneous miscarriage or missed pregnancy at a term earlier than 12 weeks, and in one family, the pregnancy was terminated for medical reasons at week 24 because the fetus had signs of skeletal dysplasia. Only two children

Table 1. Range of mutations in four genes in Russian patients with short-rib thoracic dysplasia

Proband	SRTD	Gene	Nucleotide changes	Amino acid changes	Exon	Variant described earlier
1	Type 3	<i>DYNC2H1</i>	c.5176C>T	p.Arg1726Term	34	+
			c.9044A>G	p.Asp3015Gly	57	+
2	Type 3	<i>DYNC2H1</i>	c.7972G>C	p.Gly2658Arg	49	–
			c.9044A>G	p.Asp3015Gly	57	+
3	Type 3	<i>DYNC2H1</i>	c.9044A>G	p.Asp3015Gly	57	+
			c.11341G>A	p.Gly3781Arg	78	–
4	Type 3	<i>DYNC2H1</i>	c.9044A>G	p.Asp3015Gly	57	+
			c.9710-2A>G	–	62*	+
5	Type 3	<i>DYNC2H1</i>	c.3059T>G	p. Leu1020Term	21	+
			c.8457A>G	p. Ile2819Met	53	+
6	Type 3	<i>DYNC2H1</i>	c.2T>C	p. Met1?	1	–
			c.6035C>T	p.Ala2012Val	38	+
7	Type 3	<i>DYNC2H1</i>	c.1151C>T	p.Ala384Val	8	+
			c.4429A>T	p.Lys1477Term	29	–
8	Type 11	<i>DYNC2I2</i>	c.1150G>C homozygote	p. Ala384Pro	7	–
9	Type 2	<i>IFT80</i>	c.2101G>C homozygote	p.Ala701Pro	19	+
10	Type 9	<i>IFT140</i>	c.1052G>T homozygote	p.Trp351Leu	10	–

Note: SRTD, short-rib thoracic dysplasia. * 62 — intron.

(proband 3 and 4) were diagnosed with SRTD prenatally at weeks 24 and 32 of gestation, respectively. However, in 7 of 10 cases (70%), ultrasonography of the fetus in the second and third trimesters of pregnancy detected signs of shortening of the tubular bones of the extremities in some cases associated with a curvature of the femur and polyhydramnios.

As a result of molecular–genetic analysis, four genetic variants of SRTD were identified in our patients. Seven patients were diagnosed with type 3 SRTD, and one patient each was diagnosed with type 11, 2, and 9 dysplasia caused by *DYNC2H1*, *DYNC2I2*, *IFT80*, and *IFT140* mutations, respectively. Six of the 14 nucleotide substitutions were identified for the first time. The range of detected nucleotide substitutions is presented in Table 1.

The largest number of mutations (7 missense substitutions, 3 nonsense mutations, and 1 splicing site mutation) was found in *DYNC2H1* encoding the main motor subunit of the dynein complex heavy chain and responsible for type 3 SRTD. Moreover, four variants of nucleotide substitutions were discovered for the first time. Interestingly, in 4 of the 14 alleles of *DYNC2H1*, the c.9044A>G (p.Asp3015Gly) mutation described previously as pathogenic

was found in the compound heterozygous state with other nucleotide substitutions, two of which were identified for the first time.

In one patient, a newly identified homozygous missense substitution c.1150G>C (p.Ala384Pro) was registered in *DYNC2I2* encoding another subunit of the intermediate chain of the dynein complex, which enabled us to diagnose type 11 SRTD.

Two patients had SRTD types 2 and 9 caused by *IFT80* and *IFT140* mutations, respectively, which protein products are involved in the formation of the cilia transport system. In *IFT80*, a homozygous mutation c.2101G>C (p.Ala701Pro) was identified, which was reported by Beales et al. in 2007, and a newly identified mutation c.1052G>T (p.Trp351Leu) in the homozygous state was revealed in *IFT140* [10].

Characteristics of clinical manifestations of the studied patients are summarized in Table 2.

In all probands, chest narrowing and deformity of varying severities were common clinical manifestations (Fig. 1). The syndrome of respiratory disorders in the neonatal period developed in 3 of 10 probands (30%), which required prolonged respiratory support with continuous positive airway pressure (CPAP) for proband 3. Proband 6 and 9 were

Table 2. Clinical characteristics of the studied patients

Indicator	Probands									
	1	2	3	4	5	6	7	8	9	10
	SRTD									
	Type 3	Type 3	Type 3	Type 3	Type 3	Type 3	Type 3	Type 11	Type 2	Type 9
Age	3 years	1 year	3 years	8 months	3 months	9 days	9 years	1 year	9 months	4 months
Sex	M	F	F	M	F	M	M	F	M	F
Consanguinity	-	-	-	-	-	-	-	+	+	-
Prenatal ultra-sound signs	+	+	+	+	+	+	-	-	-	+
Neonatal respiratory distress syndrome	-	-	+	-	-	+	-	-	+	-
Recurrent respiratory diseases	+	-	-	-	-	-	+	+	+	-
Height, SDS	-0.9	-1.09	-1.59	-1.34	-0.13	0.01	0.80	-3.16	-2.61	0.10
Stenothorax	+	+	+	+	+	+	+	+	+	+
Limb shortening	+	+	+	+	+	+	+	+	+	+
Brachydactyly	-	-	+	-	-	-	+	+	+	+
Polydactyly	-	-	+	-	-	-	-	-	-	-
Acetabular trident	+	+	+	+	+	+	n/a	-	+	n/a
Pigmentary retinopathy	-	-	-	-	-	-	-	-	-	+
Renal insufficiency	-	-	-	-	-	-	-	-	-	+
Basal-occipital foramen stenosis	-	-	-	-	-	-	-	-	+	-
Delayed psychomotor development	-	-	+	-	-	-	-	+	+	+

Note. SRTD, short-rib thoracic dysplasia; M, male; F, female; n/a, not available.



Fig. 1. Appearance of 10 patients with thoracic dysplasia



Fig. 2. Trident symptom on the radiograph of the left hip joint in a 3-month-old patient with thoracic dysplasia (highlighted in red)

transferred for artificial ventilation. However, proband 6 with hypoplasia of mild and severe cardiorespiratory disorders died on day 16 of life.

In four probands (1, 7, 8, and 9), respiratory disorders emerged on month 2 of life, which were associated with recurrent obstructive bronchitis and repeated pneumonia; therefore, both noninvasive and invasive lung ventilations were performed. Proband 7 underwent reconstructive surgery on the chest (decompressive thoracoplasty and osteosynthesis with titanium plates) because of persistent

tachypnea at age of 5 years, after which the respiratory function improved.

The growth rate in most patients was within the middle and lower limits of normal (from -1.59 to 0.8 SD) without significant deficit, with the exception of probands 8 and 9 with SRTD types 11 and 2 who had a postnatal decrease in growth rates of -3.16 and -2.61 SD, respectively. In all patients, a mildly pronounced limb shortening, mainly of the rhizomelic type, was noted. Brachydactyilia of the hands during clinical examination was revealed in five patients, and in proband 3, it was associated with postaxial polydactyly of both hands and the left foot.

Pelvic radiographs in seven patients showed a typical acetabular trident formed by the median prominence and two lateral spurs. The X-ray presentation of the "trident" changed somewhat within the studied patients, but it was quite apparent to a certain degree. This radiological phenomenon is caused by the peculiarity of the ossification of the supra-acetabular region. As a result of the uneven nature of this process, three "teeth" are clearly visible on pelvic radiographs in direct projection, whereas the medial "tooth" is outlined by the inner cortical layer of the sciatic notch and the lower contour of the ossified part of the ilium. The lateral "tooth" is outlined by the external supra-acetabular contour of the ossified part of the ilium and the acetabular hood. The central "tooth" is outlined by the acetabular hood and the lower contour of the ossified part of the ilium (Fig. 2). The symptom was noted at birth and was more pronounced in infancy; later, the "teeth" were smoothed out as the cartilaginous elements

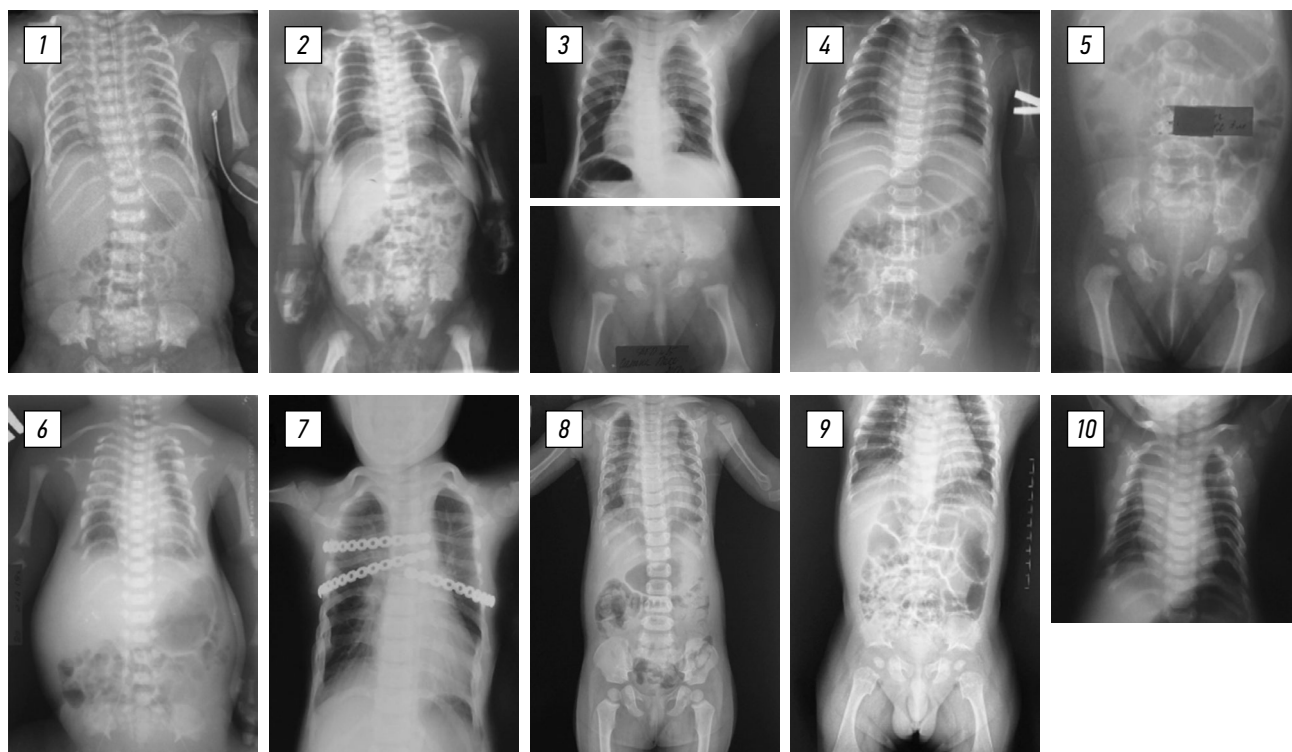


Fig. 3. Chest and hip joint radiographs of 10 patients with thoracic dysplasia

of the acetabulum ossified. Therefore, if SRTD is suspected in older children, a retrospective analysis of radiographs of the hip joints is necessary, which can help in identifying the characteristic radiological presentation and substantiate the clinical and radiological diagnoses for subsequent genetic examination.

All probands had a decrease in the transverse size of the chest and shortening and horizontal arrangement of the ribs. The chest was cylindrical or bell-shaped, and several patients had a thickening of the anterior ribs (Fig. 3). Proband 3 was diagnosed with congenital bilateral hip dislocation, which was treated conservatively with a positive effect.

Along with typical clinical manifestations, proband 10 with a newly identified *IFT140* homozygous mutation had extraskeletal manifestations of renal failure and pigmentary retinopathy and early psychomotor development delay. Patients with this combination of symptoms were first described by Mainzer and Saldino in 1970; therefore, this variant was (Mainzer–Saldino syndrome) [11]. However, in the OMIM catalog, it is designated as SRTD type 9 with or without polydactyly. The parents of this proband do not indicate direct consanguinity; however, they are Ingush by nationality and live in a small territory of the republic with a population of 515 thousand people. Chest deformity and limb shortening were registered in the girl at birth, and at 1 month of age, the absence of gaze fixation and roving eye movements became noticeable. During a hospital examination for obstructive bronchitis at age 3 months, X-ray signs of SRTD were noticed, and ultrasound examination revealed kidney cysts up to 0.2 cm in diameter and splenomegaly. In the urine tests over time, proteinuria up to 0.2 g/L was detected, and degree II bilateral medullary nephrocalcinosis, stage III chronic kidney disease, renal arterial hypertension, pigmentary retinopathy, and high degree hypermetropia of both eyes were diagnosed. At birth, low muscle tone and a psychomotor retardation were noted; the patient can sit independently from 1 year of age and can walk from the age of 2 years.

Proband 9 with type 2 SRTD caused by an *IFT80* homozygous mutation experienced severe respiratory failure and orthopedic complications from birth, including stenosis and compression of the cervical spine. In the boy with multiple lung atelectasis and an anomaly of the posterior arch of the C₁ vertebra, computed tomography revealed narrowing of the spinal canal; and at the age of 6 months, decompression surgery of the craniovertebral junction and prolonged tracheostomy were required. The psychomotor development of the child proceeded with a gross delay against the severe diffuse muscular hypotension, and he could not hold his head, roll over, and sit.

Thus, we present an analysis of the clinical, genetic, and radiological characteristics of 10 Russian patients with

types 2, 3, 9, and 11 of thoracic dysplasia with or without polydactyly caused by *DYNC2H1*, *DYNC2I2*, *IFT80*, and *IFT140* mutations. In seven patients, the disease arose as a result of homozygous and compound heterozygous mutations of *DYNC2H1*, six of which were recorded for the first time. It is assumed that there are differences in the severity of clinical manifestations and the disease course in patients with mutations in certain regions of the gene that affect the function of certain protein domains. Clinical and genetic analysis showed that in patients with *IFT80* and *IFT140* mutations, skeletal damage was more severe and could be combined with the kidney and eye pathologies, stenosis of the basal–occipital foramen, and delayed psychoverbal development.

DISCUSSION

SRTD with or without polydactyly represents a group of skeletal ciliopathy caused by impaired functioning of cilia, which play a significant role in endochondral bone formation and growth plate architectonics, in the regulation of the Hedgehog and Wnt signaling pathways necessary for the differentiation and proliferation of chondrocytes [4]. All proteins functioning in cilia are grouped into three main complexes. Complex 1 includes structural proteins of the basal body and the base of cilia, complex 2 includes motor proteins (dynein-2 and kinesin-2) that bind to transported substrates, and complex 3 consists of proteins that form the transport system of microtubules. Diseases of this group mainly arise following mutations in genes encoding the motor protein dynein or providing anterograde (from the ciliary base to the tip) and retrograde (from the ciliary tip to the base) transport along the microtubules of cilia, which is implemented using two complexes IFT-B and IFT-A [3]. The schematic structure of cilia and localization of the protein products of genes are presented in Fig. 4.

In 70% of the patients, SRTD was caused by a *DYNC2H1* mutation responsible for the occurrence of type 3 disease, which corresponds to data obtained by other authors, who registered mutations in this gene in 33%–61% of the patients [4, 7, 12]. *DYNC2H1* consists of 90 exons and encodes the main subunit of the dynein complex, cytoplasmic dynein-2 heavy chain 1, consisting of 4314 amino acids. Its domain structure includes an N-terminal region-1 (DHC_N1) and a linker region-2 (DHC_N2), six ATP-hydrolyzing domains, and a core and a C-terminal domains [4]. In seven patients, we identified 11 mutations, four of which were detected for the first time (Fig. 5). Four of the seven probands had the previously described mutation c.9044A>G (p.Asp3015Gly), which is quite common in patients with SRTD from European countries. Thus, in 2009, Dagoneau et al. revealed this mutation in patients from France, Schmidts et al. detected it in 2013 in patients from Holland, and Čechová et al. registered it in 2019 in a Czech patient [12–14]. In 2018, Zhang et al.

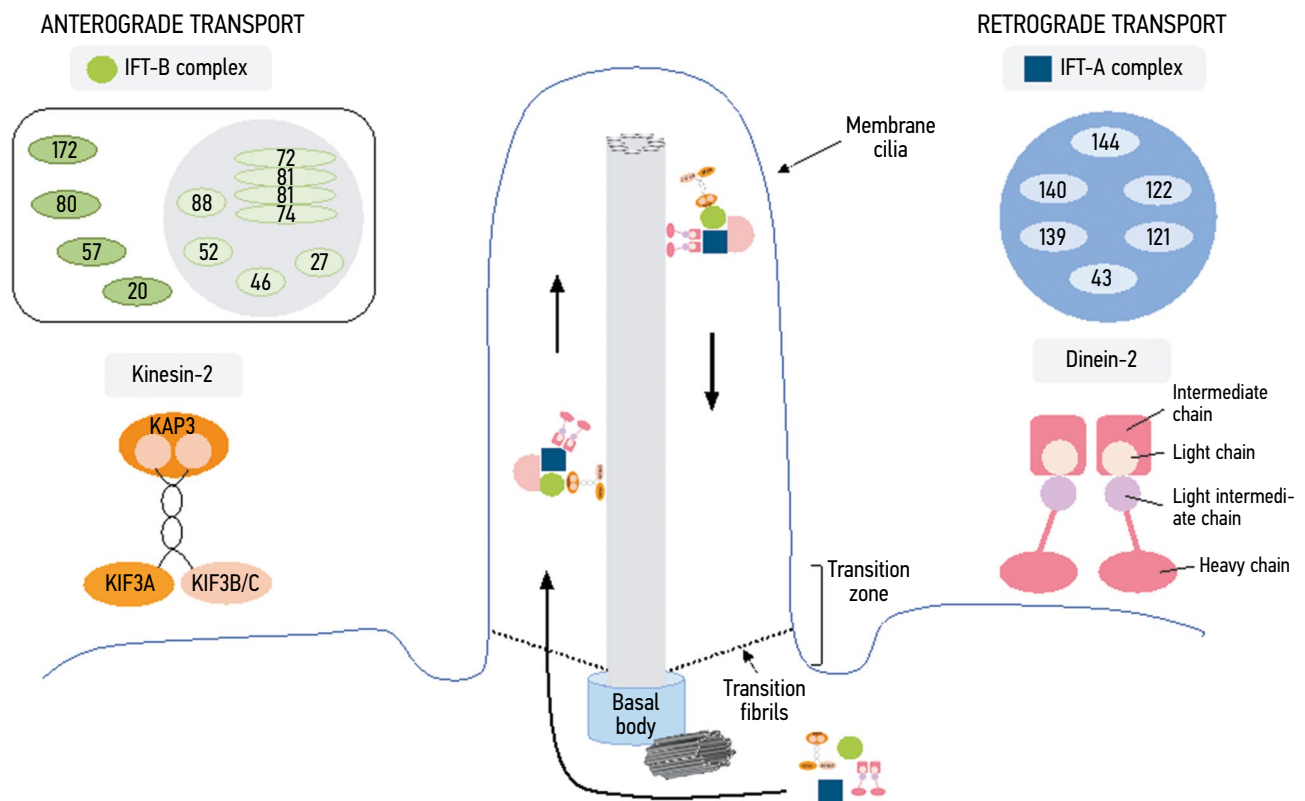


Fig. 4. Diagram of the cilium structure

detected this mutation in five newborns of European origin with SRTD from the archive of the International Registry of Skeletal Dysplasia [4]. Functional analysis showed that Asp3015Gly substitution leads to the destruction of the hydrogen bond between two α -helices of the *DYNC2H1* protein, its conformational change, impairing the ability of the motor complex to attach to microtubules [13]. Although the missense mutation c.9044A>G (p.Asp3015Gly) was repeatedly identified in patients with SRTD, it was not registered in a homozygous state in any patient, including in our sample, which is presumably a genetically lethal variant incompatible with fetal development.

SRTD caused by *DYNC2H1* mutations is characterized by varying severities, from mild to severe forms, leading to lethal outcome at an early age due to severe lung impairment. The severity of clinical manifestations may be associated with the different effects of mutations on dynein function. Thus, in proband 7, a 9-year-old boy with reconstructive surgery on the chest, p.Ala384Val and p.Lys1477Term mutations disrupt the function of the N-terminal domains of the heavy chain, which are involved in homodimerization and binding to auxiliary subunits of the dynein complex [15]. Mutation 1 has been described in patients with perinatally lethal short-rib syndrome with polydactyly, whereas mutation 2 was discovered by us for the first time [16–18]. In four probands (1, 3, 5, and 6) in one of the alleles, missense and nonsense mutations in the ATP-hydrolyzing domains were identified, and in one of these cases, with the p. Ala2012Val mutation,

lethal outcome occurred in the neonatal period. It is assumed that the localization of amino acid substitutions in the AAA domains can prevent ATP hydrolysis with energy conversion for the movement of complexes along microtubules [19].

The viability of patients depended on respiratory complications, as they did not have extraskelatal manifestations of ciliopathies, which confirms the important genotype–phenotype correlation in the presence of *DYNC2H1* mutations, but necessitates long-term follow-up because of the risk of their development at a later age [7, 12].

Type 11 SRTD, caused by *DYNC2I2* mutations, is the second most common in this group of diseases, accounting for 10% of all cases described in the literature [20]. However, in our sample, a *DYNC2I2* mutation was revealed in only one patient. *DYNC2I2* encodes a protein of 536 amino acids, which is a member of the protein family with WD repeats and contains five WD40 domains (repeats of 40 amino acids) that promote the formation of heterotrimeric multiprotein complexes [21]. The protein product of the gene is an intermediate chain of the dynein motor complex, which main function is to recognize and bind transported substrates.

In 2013, Huber et al. first identified *DYNC2I2* mutations, after which it became known that most patients with this type did not survive after the neonatal period because of severe respiratory disorders [21]. Proband 8, a girl aged 1 year 4 months, whose parents were each other's second cousins, had a new mutation in the homozygous state in exon 7 of

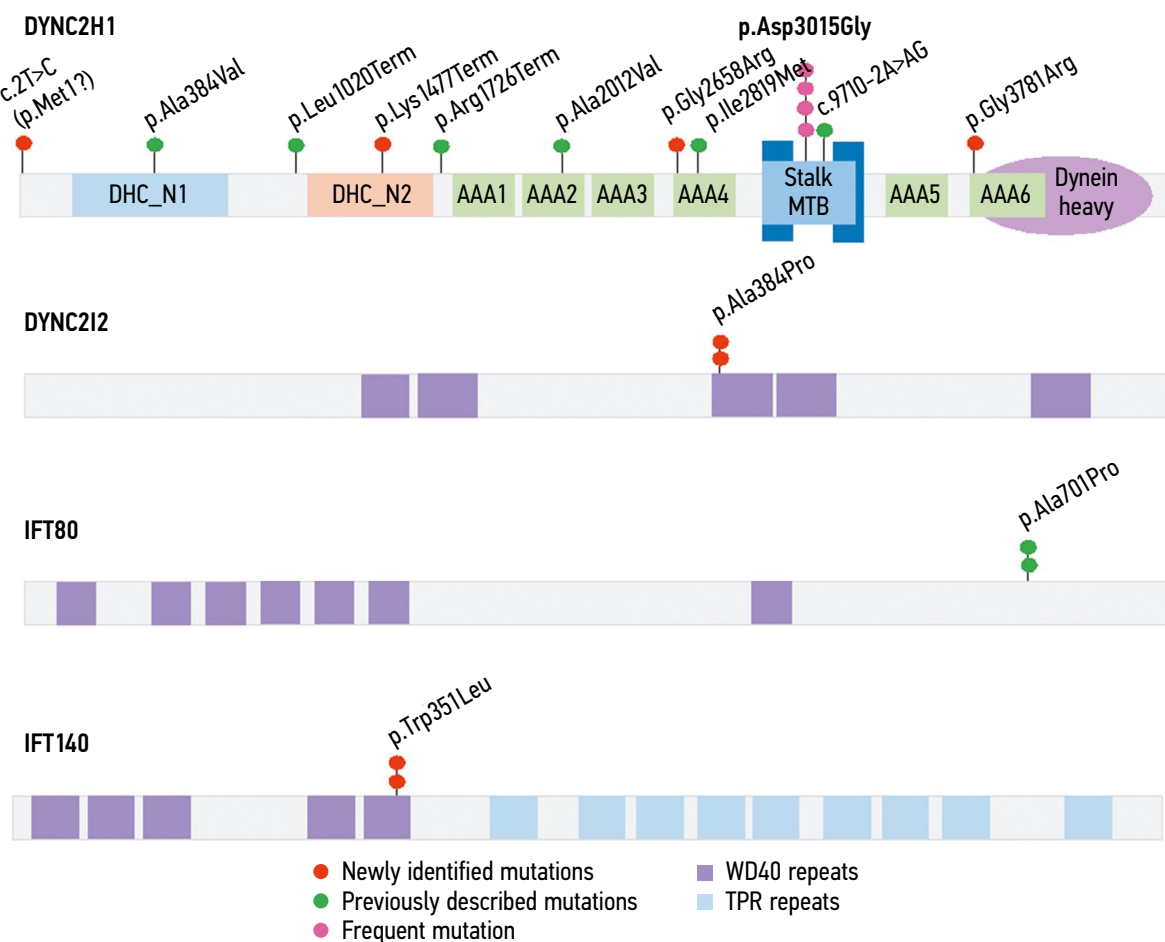


Fig. 5. Localization of amino acid substitutions in the domains of *DYNC2H1*, *DYNC212*, *IFT80*, *IFT140* proteins in Russian patients with short-rib thoracic dysplasia

DYNC212, c.1150G>C (p.Ala384Pro). The child was born from the second pregnancy, and her mother's first pregnancy was terminated at week 24 because the fetus had signs of skeletal dysplasia. The disease course in the proband was significantly severe because of worsening respiratory disorders caused by pneumonia and lung hypoplasia, for which the child was repeatedly hospitalized in the intensive care unit. Despite ongoing therapy, the child died at age 2 years 8 months. The p.Ala384Pro missense substitution in *DYNC212* in the proband changes the amino acid sequence of WD40 repeats, which, according to Li and Roberts, can disrupt protein–protein interactions mediated by these repeats and binding of protein “loads” [22] (Fig. 5).

IFT80 mutations cause a rare SRTD variant with or without type 2 polydactyly. Mutations in this gene were first identified by Beales et al. in 2007 in three consanguineous families [10]. Currently, 16 *IFT80* mutations are known [23]. *IFT80* encodes a 777-amino acid protein that is a component of the IFT-B anterograde transport complex. The homozygous mutation c.2101G>C (p.Ala701Pro) that were have found in proband 9 was described by Beales et al. in 2007 in two siblings in a consanguineous Pakistani family [10] (Fig. 5). The parents of proband 9 were also related by blood; their

history includes a case of neonatal death in a sibling of the proband with similar symptoms. The boy was diagnosed with a syndrome of respiratory disorders at birth, for which he received artificial lung ventilation for 20 days, followed by respiratory support with CPAP, and at age 6 months, he underwent urgent surgery because of a pronounced stenosis of the basal–occipital foramen with cervico–medullary compression, followed by an increase in respiratory failure and imposition of a tracheostomy. A similar complication in the form of atlanto–axial instability with spinal cord compression was noted by Tüysüz et al. in 2009 in a 4.5-year-old Turkish girl with a homozygous mutation p. H105Q in *IFT80*, which has not been previously reported in SRTD [24]. These data may jointly indicate the peculiarities of the course of type 2 SRTD.

IFT140 mutations cause another rare SRTD type 9, previously described as Mainzer–Saldino syndrome or conorenal syndrome, due to a characteristic radiographic finding in the form of cone-shaped epiphyses of the metacarpal bones and phalanges after the first year of life [11, 25]. In addition to signs of thoracic dysplasia, patients with this type have pronounced extraskeletal manifestations of chronic renal failure and severe pigmentary retinopathy that occur in early

childhood. Several patients also have short stature, cerebellar ataxia, and hepatic fibrosis.

IFT140 consists of 31 exons and encodes a 1462-amino acid protein containing five WD40 repeats and nine tetratricopeptide repeats (TPR), which provide protein–protein interactions and are involved in the retrograde transport complex IFT-A of cilia [26]. Proband 10 had a previously undescribed homozygous mutation in exon 10 c.1052G>T (p.Trp351Leu), which disrupts the functions of WD repeats (Fig. 5). Severe retinal dystrophy after birth was the initial manifestation of this SRTD type, and skeletal signs of thoracic dysplasia and symptoms of renal failure were revealed in the girl later with recurrent respiratory diseases. Symptoms of an early degenerative retinal lesion at the initial disease stage became the reason for the suspicion of Leber's congenital amaurosis in the proband. Although in rare cases, retinitis pigmentosa type 80 may be an isolated allelic variant of this disease group caused by *IFT140* mutations. All known cases of type 9 SRTD were accompanied by typical skeletal features and the development of end-stage renal failure in children in the first decade of life [26, 27].

CONCLUSION

Clinical genetic analysis was performed in 10 patients with four genetic variants of skeletal ciliopathies (SRTD). Six newly identified nucleotide substitutions were identified, and the mechanism of their influence on the functions of the protein product was discussed. As in the previously described patients, in the sample analyzed, more than half of the cases were caused by a *DYNC2H1* mutation that caused type 3 SRTD. The main clinical and radiological manifestations of this variant are characterized by a bell-shaped deformity of the chest with short ribs, resulting in respiratory disorders, limb shortening, and brachydactylia, the presence of the so-called trident in the iliac acetabulum. The differences in the severity of clinical manifestations and disease course

in patients with mutations in certain regions of the gene, which have a different effect on the function of its protein product, have been revealed. Stenosis of the basal–occipital foramen was noted in patients with type 2 SRTD caused by *IFT80* mutations. The multiple-organ damage in patients with type 9 SRTD due to *IFT140* mutations, whose symptoms of skeletal dysplasia were combined with kidney, retina, liver, and brain pathologies, has been confirmed. The results of the molecular–genetic study expand the range of mutations in *DYNC2H1*, *DYNC212*, and *IFT140* that cause SRTD types 3, 11, and 9 and confirm the importance of exome sequencing as the main method for identifying mutations in the genetically heterogeneous SRTD group.

ADDITIONAL INFORMATION

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Author contributions. T.V. Markova, V.M. Kenis, and I.A. Kholmkin created the study design, reviewed the literature, and wrote and edited the text of the article. E.V. Melchenko, D.V. Osipova, N.A. Semenova, M.S. Petukhova, and N.A. Demina collected and processed the clinical material and analyzed the data obtained. T.S. Nagornova performed the laboratory molecular–genetic diagnostics, analyzed the research results, and wrote the text of the article. E.Yu. Zakharova, E.L. Dadali, and S.I. Kutsev developed the study concept and edited the article text.

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