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Original Study Article

Principles of the differential diagnosis of achondroplasia and pseudoachondroplasia

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BACKGROUND: Achondroplasia and pseudoachondroplasia are hereditary systemic skeletal dysplasias characterized by a certain similarity of clinical manifestations; however, they have different etiopathogenetic mechanisms and confirmation methods for molecular genetic diagnosis. Their common phenotypic features often make differential diagnosis difficult during the clinical examination of patients, planning DNA diagnostics, and appropriate time detection of neurosurgical and orthopedic complications.

AIM: This study aimed to identify differential diagnostic criteria for achondroplasia and pseudoachondroplasia and optimize the strategy for their molecular genetic diagnosis.

MATERIALS AND METHODS: A comprehensive examination of 76 children from 74 unrelated families aged 1 month to 18 years with phenotypic signs of achondroplasia and pseudoachondroplasia was conducted. To clarify the diagnosis through genealogical and amnestic analysis, clinical and neurological examination data according to the standard method and radiographic data were used. Molecular genetic confirmation of diseases was conducted by searching for hotspot mutations in the *FGFR3* gene, assessing the number of GAC repeats located in exon 13 of the *COMP* gene, and new-generation sequencing of the target panel consisting of 166 genes responsible for hereditary skeletal pathology.

RESULTS: Based on a comparative analysis of the specific phenotypic characteristics, the criteria for the differential diagnosis of achondroplasia and pseudoachondroplasia were identified. The leading signs of achondroplasia are disproportionate nanism from birth, macrocrania, and facial dysmorphism, which are not specific to pseudoachondroplasia. Certain radiological features are essential in the differential diagnosis of pseudoachondroplasia, which should be considered when referring to patients for molecular genetic analysis. A deletion of the GAC repeat c.1417_1419del in the *COMP* gene was identified in 27% of patients with pseudoachondroplasia. Thus, the analyses of these two mutations in *FGFR3* and *COMP* were conducted first. In the absence of target mutations, further diagnostic search should be continued with a target panel consisting of 166 genes responsible for hereditary skeletal pathology or whole-exome sequencing.

CONCLUSIONS: The analysis of the clinical, radiological, and molecular genetic characteristics of patients with achondroplasia and pseudoachondroplasia, together with the literature data analysis, made it possible to clarify the differential diagnostic criteria for these diseases and optimize the algorithm for their molecular genetic diagnosis.

Keywords: achondroplasia; pseudoachondroplasia; *FGFR3* gene; *COMP* gene.

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Оригинальное исследование

Принципы дифференциальной диагностики ахондроплазии и псевдоахондроплазии

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Обоснование. Ахондроплазия и псевдоахондроплазия — наследственные системные скелетные дисплазии, характеризуемые определенным сходством клинических проявлений, но с различными этиопатогенетическими механизмами. Для их молекулярно-генетической диагностики применяют разные способы. Общие фенотипические особенности этих заболеваний часто затрудняют их дифференциальную диагностику при клиническом осмотре пациентов, планирование ДНК-диагностики, своевременное выявление нейрохирургических и ортопедических осложнений.

Цель — определить дифференциально-диагностические критерии ахондроплазии и псевдоахондроплазии и оптимизировать стратегию их молекулярно-генетической диагностики.

Материалы и методы. Проведено комплексное обследование 76 детей из 74 неродственных семей в возрасте от 1 мес. до 18 лет с фенотипическими признаками ахондроплазии и псевдоахондроплазии. Для уточнения диагноза использовали генеалогический анализ, данные анамнеза, клиническое обследование, неврологический осмотр по стандартной методике, рентгенографию. Молекулярно-генетическое подтверждение диагноза заболеваний осуществляли путем поиска частых мутаций в гене *FGFR3*, оценки количества GAC-повторов, локализованных в экзоне 13 гена *COMP*, и секвенированием нового поколения таргетной панели, состоящей из 166 генов, ответственных за развитие наследственной скелетной патологии.

Результаты. На основании сравнительного анализа особенностей фенотипических характеристик пациентов с ахондроплазией и псевдоахондроплазией уточнены критерии их дифференциальной диагностики. При ахондроплазии ведущими признаками были диспропорциональный нанизм с рождения, макрокрания и лицевые дизморфии, которые нехарактерны для псевдоахондроплазии. Существенное значение в дифференциальной диагностике псевдоахондроплазии имеют специфические рентгенологические особенности, которые необходимо учитывать при направлении пациентов на молекулярно-генетический анализ. Подтверждено наличие мажорной мутации c.1138G>A в гене *FGFR3* у абсолютного большинства пациентов с ахондроплазией, а у 27 % пациентов с псевдоахондроплазией обнаруживали делецию повтора GAC в гене *COMP* (c.1417_1419del). На основании полученных результатов сделано заключение о целесообразности первоочередного анализа этих двух мутаций в генах *FGFR3* и *COMP*. При отсутствии искомых мутаций диагностический поиск следует продолжить с помощью таргетной панели генов, состоящей из 166 генов, ответственных за развитие наследственной скелетной патологии или полное секвенирование экзома.

Заключение. Анализ клинико-рентгенологических и молекулярно-генетических характеристик в выборках пациентов с ахондроплазией и псевдоахондроплазией в совокупности с изучением литературных данных позволил уточнить дифференциально-диагностические критерии этих заболеваний и оптимизировать алгоритм их молекулярно-генетической диагностики.

Ключевые слова: ахондроплазия; псевдоахондроплазия; ген *FGFR3*; ген *COMP*.

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BACKGROUND

Achondroplasia (AC) and pseudoachondroplasia (PSAC) are hereditary diseases from the group of skeletal dysplasias, characterized by a certain similarity of clinical manifestations, but with different etiopathogenetic mechanisms. These diseases have varied prevalence. One case of AC per 25,000–30,000 populations and one case of PSAC per 60,000 people are registered [1, 2]. Both diseases are inherited in an autosomal dominant manner, with most cases being sporadic [3]. Phenotypic manifestations of diseases are characterized by disproportionate dwarfism caused by rhizomelic limb shortening, limb deformities, brachydactyly, joint hypermobility, and muscular hypotonia [2, 3]. In the majority of patients with both AC and PSAC, hypermobility of the interphalangeal joints of the hands is combined with limited elbow joint extension. These common phenotypic signs often make it difficult to differentiate AC from PSAC during the clinical examination of patients and planning additional examinations, including the choice of confirmatory DNA diagnostic methods.

More than 97% of all AC cases are caused by the c.1138G>A mutation in the *FGFR3* gene located on chromosome 4p.16.3 [4]. The gene product is the fibroblast growth factor receptor, which negatively influences cell proliferation by shortening the proliferative phase and accelerating the terminal phase of cell division [5]. The gene is expressed predominantly on the membrane of chondrocytes and neurons [6, 7].

While patients with AC were known several centuries ago, PSAC was first described by Pierre Maroteaux and Maurice Lamy in 1959 [8]. The etiological factor of the disease was established only in 1995 when Briggs et al. first identified *COMP* mutations in patients with PSAC and multiple epiphyseal dysplasias [9]. The gene is located on chromosome 19p13.11 and contains 19 exons. It encodes a pentameric glycoprotein of the thrombospondin family [10]. This protein was originally isolated from the cartilage and characterized as an "oligomeric cartilage matrix protein." It's mainly localized in the articular cartilage and in proliferating and hypertrophic chondrocytes of the growth plate of tubular bones, which promote endochondral ossification and articular cartilage development [11, 12]. In patients with PSAC, 90% of mutations are located in exons 8–14, encoding a protein domain that consists of amino acid residues grouped into eight consecutive T3 repeats [13].

Thus, different methods of DNA analysis for confirmatory molecular–genetic diagnostics of AC and PSAC, the need for timely detection of neurosurgical and orthopedic complications, and the use of methods for surgical correction of life-threatening complications in patients with AC, and the fact that in recent years, pathogenetic treatment is being developed for this disease necessitate a thorough analysis of the phenotypic features and radiological characteristics of diseases in representative samples of patients.

This study aimed to determine the differential diagnostic criteria for AC and PSAC and optimize the strategy for their molecular–genetic diagnostics.

MATERIALS AND METHODS

Seventy-six pediatric patients from 74 unrelated families, aged 1 month to 18 years, with phenotypic signs of AC and PSAC, were comprehensively examined. To clarify the diagnosis, genealogical analysis, anamnesis data, clinical examination, neurological examination according to the standard method with psycho-emotional assessment, and radiography were used. Molecular–genetic confirmation of AC and PSAC was based on the results of new-generation sequencing of a targeted panel consisting of 166 genes responsible for the development of hereditary skeletal pathology. DNA analysis was performed on a new-generation sequencer Ion S5. For sample preparation, ultramultiplex polymerase chain reaction was used, coupled with subsequent sequencing (AmpliSeq). The number of copies of the GAC repeat located in exon 13 of *COMP* (NM_000095.3) was estimated by analyzing the length polymorphism of amplification fragments from primers of complementary sequences of exon 13, and results were detected by polyacrylamide gel electrophoresis. To search for *FGFR3* mutations (NM_000142.5), allele-specific ligase-dependent amplification was used with the visualization of the results by polyacrylamide gel electrophoresis.

Genomic DNA was isolated from whole blood using the DNAEasy kit (QiaGen, Germany) according to the manufacturer's standard protocol. DNA and library concentration was measured on a qubit2.0 instrument using reagents (qubit BR and qubit HS) from the manufacturer according to the standard protocol. Sample preparation was performed according to a method based on the multiplex polymerase chain reaction of target DNA regions. Next-generation sequencing was performed on an Ion Torrent S5 sequencer, with an average coverage of at least 80, and target areas with coverage of 90%–94% or higher. For the annotation of the variants identified, the nomenclature presented on the site http://varnomen.hgvs.org/recommendations/DNA, version 2.15.11, was used. Sequencing data were processed using a standard automated algorithm by Ion Torrent.

To assess the population frequencies of the identified variants, the samples of the 1000 Genomes Project, ESP6500, and The Genome Aggregation Database v2.1.1 were used, and to assess the clinical significance of these variants, the OMIM database and HGMD® Professional 2021.3 pathogenic variants database were used. Genetic variants were evaluated in accordance with international recommendations

for the interpretation of data obtained by massively parallel sequencing [14].

The variants revealed in the probands and genotyping of siblings and parents were validated by direct automatic Sanger sequencing on an ABIPrism 3500xl instrument according to the manufacturer's protocol (Applied Biosystems). The primer sequences were selected according to the reference sequence of the target regions of *COMP*.

The anthropometric parameters of patients, taking into account SDS indicators, were evaluated using approved charts of the World Health Organization. Statistical processing of the results was performed using the standard statistical package Statistica 10 and Microsoft Excel. The hypothesis about the differences between the two studied populations was tested using Student's t-test. Values are presented as mean ± standard deviation (SD). Differences were considered statistically significant at $p < 0.05$. For qualitative attributes, a frequency analysis of indicators (%) was performed.

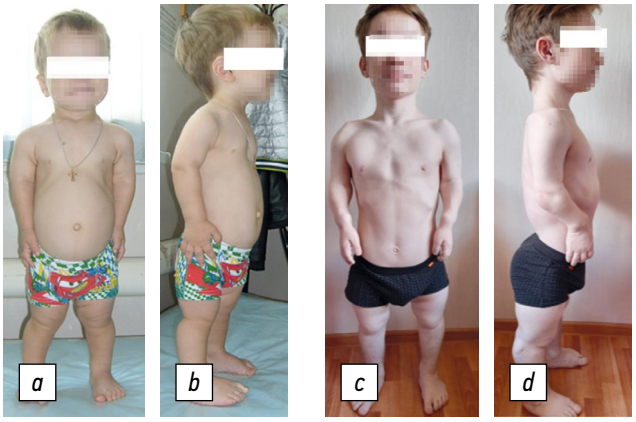

Fig. 1. Appearance of patients with achondroplasia (*a, b*) and pseudoachondroplasia (*c, d*). Both patients have a disproportionate short stature with limb shortening, chest deformity, incomplete extension of elbow joints, lower extremity deformities, and brachydactyly, and macrocrania (an increase in cranial size and frontal and parietal protuberances) and facial dysmorphism (midface hypoplasia) were noted only in a patient with achondroplasia

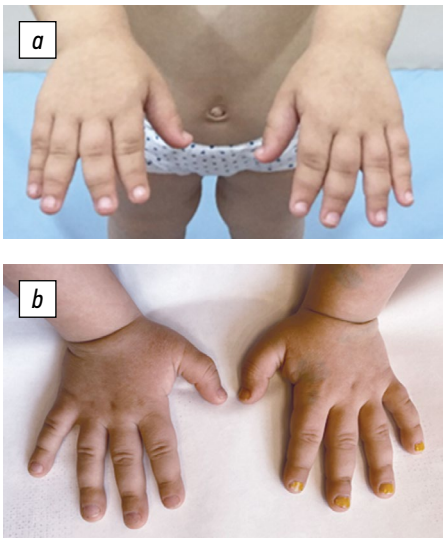

Fig. 2. Appearance of the hands of patients with achondroplasia (*a*) and pseudoachondroplasia (*b*): both patients had brachydactyly. Isodactyly (comparable length of fingers) and ectrosyndactylia symptoms (divergence of the phalanges of the fingers, more pronounced between the terminal phalanges of the fingers II–III and III–IV) were noted only in a patient with achondroplasia

RESULTS

To identify the differential diagnostic signs of AC and PSAC, the phenotypic, radiological, and molecular–genetic characteristics of patients with AC and PSAC aged from 1 month to 18 years were analyzed.

AC caused by *FGFR3* mutations was diagnosed in 50 unrelated patients aged 1 month to 12 years (16 boys and 34 girls). Moreover, 96% of cases were sporadic, and in 4% of families, the disease was inherited from one of the parents. In all patients, phenotypic manifestations of the disease were noted immediately after birth; however, in 90% of cases, the disease was suspected even during an ultrasound examination of the fetus in the second and third trimesters of pregnancy based on the detection of the shortening of the tubular bones of the extremities. The mean height at birth was 48.94 ± 0.7 cm (26% of newborns were below the median of the World Health Organization data standard), and the head circumference was 36.6 ± 0.6 cm (it exceeds 2 SD in 70% of newborns). The characteristic clinical symptoms of AC in newborns were muscle hypotension and a decrease in chest size, which in 20% of cases caused respiratory disorders. For their relief, assisted lung ventilation was used, and in the case of secondary pneumonia, artificial ventilation of the lungs was used.

The main phenotypic characteristics in patients with AC were disproportionate dwarfism with rhizomelic limb shortening, macrocrania, enlarged anterior fontanel, protruding forehead, flattening of the midface, dented nose bridge, short nose with anteverted nostrils, narrow chest, and isobrachydactyly with fan-shaped finger configuration in the form of a trident (Figs. 1 and 2).

Growth retardation progressed significantly with age in patients with AC. At the age of <1 year, the deviation of height from the age norm ranged from –0.51 to –5.67 (average –3.02 SD), and at the age of >1 year, it was from –2.76 to –6.66 (average –5.03 SD). Moreover, head circumference indices in patients with AC were above the average values with +2.59 SD (from +0.7 to +6.65). All patients with AC showed a delay in the rate of early motor development. Most of them acquired the ability to walk independently only at the age of 17 months. In 95% of pediatric patients, already in the first year of life, dynamic kyphosis of the thoracolumbar junction occurred, which gradually decreased by the time of independent walking. A typical clinical manifestation was

hypermobility in the interphalangeal joints of the hands, along with a limited extension in the elbow joints. In 74% of pediatric patients, varus deformity of the lower legs developed after 1 year, and in 100% of pediatric patients, lumbar hyperlordosis developed (Fig. 3). On radiographs of the spine in pediatric patients with AC, as a rule, already at the age of 1 year, thoracolumbar kyphosis was detected, associated by a pronounced anterior wedging of the vertebral bodies at its apex and smoothing of the physiological thoracic kyphosis and increased lumbar lordosis (Fig. 3*a*). In PSAC, abnormal ossification of the apophyses of the vertebral bodies dominates with the formation of linguiform protrusions of their anterior sections, and the increase in lumbar lordosis is characterized by moderate magnitude, primarily due to muscle weakness, rather than structural changes, as in AC (Fig. 3*b*).

In 7 (14%) patients with AC, computed or magnetic resonance imaging of the brain registered signs of moderately severe external–internal hydrocephalus, which grew intensively in only one patient, which required ventriculoperitoneal shunting at the age of 1 year 3 months. In 13 pediatric (26%) patients, stenosis of the foramen magnum was detected in early childhood, and surgical decompression was performed at the level of the craniovertebral junction.

Characteristic signs on radiographs allowing confirmatory diagnostics of AC in young pediatric patients were as follows: a square shape of the iliac wings, a flat horizontal acetabulum, a narrow sciatic notch, narrowing of the interarch distance in the lumbar spine, short tubular bones with moderate metaphyseal expansion, radiolucency of the proximal femur, and brachydactyly with an X-ray presentation of ectrosyndactylia (Fig. 4). This radiological symptom is based on the peculiarity of the ossification of the supraacetabular region, resulting in the formation of "teeth." Three "teeth" formed by the cortical layer of the ischial notch, contours of the ossified part of the ilium, and arch of the acetabulum are visible on radiographs.

As a result of the molecular–genetic analysis in 98% of patients with AC, a nucleotide substitution of guanine for arginine or cytosine at position 1138 of *FGFR3* was detected, c.1138G>A (92%) or c.1138G>C (6%), resulting in the same amino acid substitution of arginine for glycine at position 380 (p. Gly380Arg) of the protein molecule. In one child, a rareR nucleotide substitution c.1123G>T (p. Gly375Cys) was identified, which was previously described in patients with AC [15–17].

The sample of patients with PSAC consisted of 26 patients from 24 unrelated families (11 boys and 15 girls) aged 1 year to 18 years. In 69% of cases, patients were only family members with this disease, and in 31% of cases, the segregation of the disease was noted in two generations. At birth, no distinct clinical characteristics were noted in the sample of patients with PSAC. The parameters of height and head

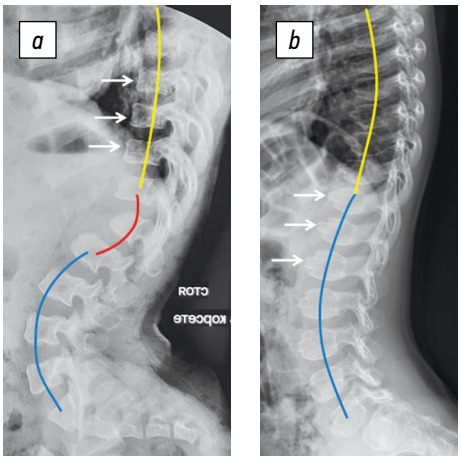

Fig. 3. Radiographs of the thoracic and lumbar spine in the lateral view of patients with achondroplasia (*a*) and pseudoachondroplasia (*b*): *a,* physiological ossification of the apophyses of the vertebral bodies with square contours of the vertebrae (white arrows), flattened thoracic kyphosis (yellow line), pathological thoracolumbar kyphosis (red line), and enhanced lumbar lordosis (blue line); *b,* abnormal ossification of the apophyses of the vertebral bodies with linguiform protrusions of the anterior parts of the vertebrae (white arrows), physiological value of thoracic kyphosis (yellow line), and moderate increase in lumbar lordosis (blue line)

circumference of the newborns corresponded to the standard values; thus, the average height was 51.46 ± 1.7 cm, and the head circumference was 34.2 ± 0.7 cm. Disease onset in patients with PSAC was registered at the age of 1–3 years with growth retardation and waddling (goose) gait associated with muscular hypotonia and hypermobility of the joints, rapid fatigue when walking, difficulty climbing stairs, which was initially regarded as a neuromuscular disease in 15% of cases, and arthralgia occurring in 54% of patients, mainly in the joints of the lower extremities, was the reason for ruling

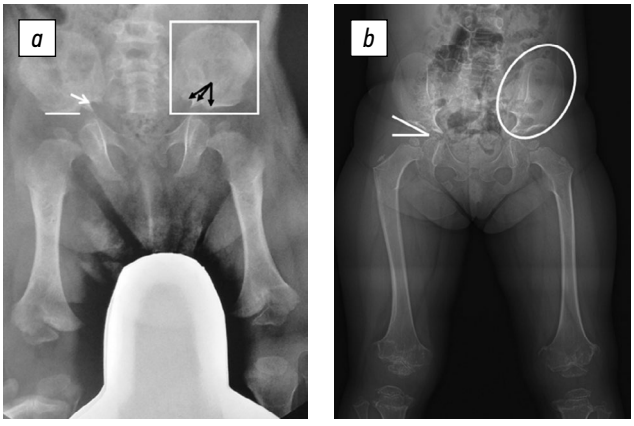

Fig. 4. Radiographs of the hip joints and femoral bones in the frontal view of patients with achondroplasia (*a*) and pseudoachondroplasia (*b*): *a,* horizontal position of the acetabular hood (white line), narrowed sciatic notch (white arrow), ectrosyndactylia (black arrows), and square outlines of the iliac wings (white outline); *b,* skewness of the acetabular hood (white lines) and oval outlines of the iliac wings (white outline)

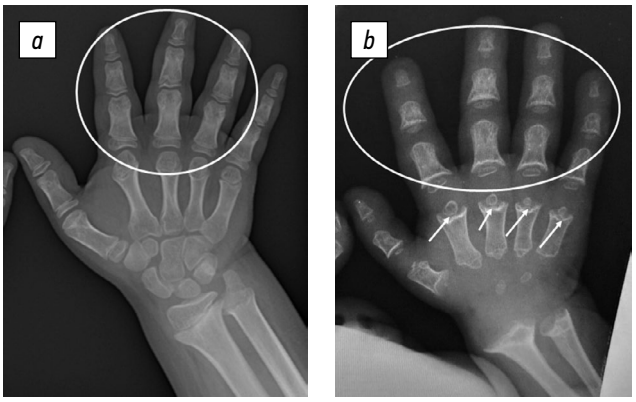

Fig. 5. Radiographs of the hands of a patient with achondroplasia (*a*) and pseudoachondroplasia (*b*): moderate ulnar deviation of the hand and brachydactyly in both patients (marked with a white outline), and shortening of the metacarpal bones with scyphoid expanded metaphyses, and small rounded ball-in-socket epiphyses in patients with pseudoachondroplasia (white arrows)

out arthritis of unknown etiology or undifferentiated connective tissue dysplasia. The average age of the beginning of independent walking was 1 year and 2 months.

The decrease in height varied significantly from –0.25 SD to –10.62 SD, depending on the age of the patient and disease severity. In early childhood, all patients had typical clinical manifestations, including proximal limb shortening, brachydactyly, widening of the wrist area, ulnar deviation of the hands, and hypermobility of large and small joints, except for the elbows, where the extension was limited already in the first year of life. Progressive deformity of the lower extremities, predominantly varus (58% of patients) and less often valgus (35% of patients) or in combination (windswept), when varus deformity was formed on one limb and valgus deformity was formed on the other limb (7% of patients), appeared in the second or third year of life. Lumbar hyperlordosis was detected in all cases, whereas severe scoliosis, for which surgical treatment was performed in adolescence, was revealed in one case (Fig. 3). PSAC was indicated in the referring diagnosis only in 60% of cases, whereas in the remaining patients, rickets-like disease or AC was assumed.

The diagnostics of PSAC was largely facilitated by radiographic data analysis, which revealed specific changes such as a delay in the ossification of the apophyses of the vertebral bodies in childhood, which determined their characteristic coronoid shape on radiographs of the spine in the lateral view, and shortening of the tubular bones with a generalized delay in the ossification of the epiphyses, manifested by a decrease in their size, irregular shape, and uneven contours. In addition, a pronounced involvement of the metaphyses was typical, as in their expansion with uneven (wavy and "corroded") contours. On radiographs of the hands, a characteristic presentation, namely, shortening of the metacarpal bones with scyphoid expanded metaphyses and small rounded ball-in-socket epiphyses, was noted [18] (Fig. 5).

As a result of molecular–genetic analysis, 17 pathogenic variants in *COMP* were identified, including eight variants for the first time. Missense variants were found in 73% of cases, and deletion without reading frame shift was detected in one of the five GAC repeats in exon 13 encoding aspartic acid, namely c.1417_1419del (p. Asp473del), in 27% of patients. In previously examined samples, this mutation occurred in 16%–30% of cases, which corresponds to our results [19, 20]. The localization of amino acid substitutions in individual domains of the COMP protein is presented in Fig. 6.

Most pathogenic variants in patients with PSAC were localized in the region of exons 8–14 encoding the domain of calmodulin-like repeats type 3 (CLR/T3). Interestingly, nucleotide transversions or transitions at position 1309 of the nucleotide sequence, not previously described, caused two amino acid substitutions of aspartic acid in the calcium-binding repeat 6 T36 in two patients, namely, c.1309G>T (p. Asp437Tyr) and c.1309G>C (p. Asp437His), and this indicates the important role of asparagine at position 437 of the protein molecule. A missense mutation leading to the replacement of a highly conserved glycine residue

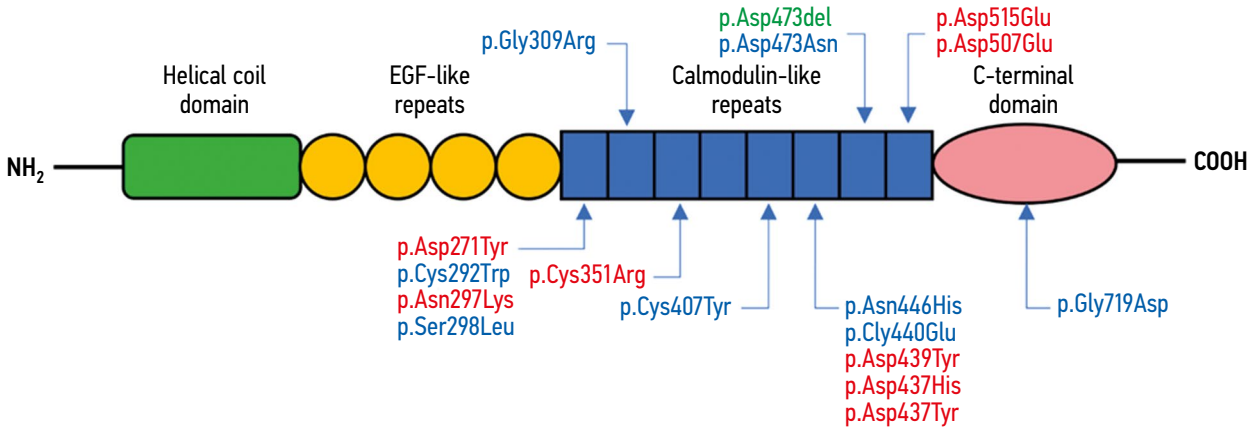

Fig. 6. Domain-specific distribution of pathogenic variants in *COMP*. Newly identified variants in *COMP* are highlighted in red, previously described variants are highlighted in blue, and frequent mutations are highlighted in green

Table 1. Comparative analysis of anamnestic and phenotypic signs in patients with achondroplasia and pseudoachondroplasia

Symptom	Achondroplasia	Pseudoachondroplasia
Short stature from birth	Yes	No
Macrocephaly	Yes	No
Dented nose bridge and midface hypoplasia	Yes	No
Hydrocephalus	Yes	No
Rhizomelic limb shortening	Yes	Yes
Muscular hypotension	Yes	Yes
Narrow chest and paradoxical respiration	Yes	No
Varus deformity of the lower legs	Yes	Yes
Shape of the hands	Ectrosyndactylia of the hands and brachydactyly	Brachydactyly and ulnar deviation
Elbow joint stiffness	Yes	Yes
Hypermobility of the interphalangeal joints	Yes	Yes
Waddling gait	Yes	Yes
Pain in the joints of the extremities	In older childhood (knee)	From younger childhood (knee, hip, ankle, and wrist)

in T32 c.925G>C (p. Gly309Arg) was revealed in two more probands. One pathogenic variant, c.2156G>A (p. Gly719Asp), was detected in the region of the C-terminal globular domain, and no variants were identified in exons 1–7 encoding coiled-coil domains and T2 repeats (EGF-like repeats).

Thus, a comparative analysis of anamnestic, phenotypic, and radiological data of patients with AC and PSAC enabled us to the define criteria for the differential diagnostics of these two diseases, which must be considered when referring to patients for molecular–genetic analysis (Table 1).

Based on the analysis of anamnestic and clinical data, similar clinical symptoms of AC and PSAC were revealed, such as disproportionate dwarfism due to rhizomelic limb shortening, lower limb deformity, elbow joint stiffness, and interphalangeal joint hypermobility, brachydactyly, and moderate diffuse muscular hypotension. Moreover, anamnestic characteristics and phenotypic aspects that are revealed during the clinical examination can be emphasized. Thus, patients with AC have growth reduction and rhizomelic limb shortening since birth, whereas in patients with PSAC, these signs become noticeable after the age of 1 year. Patients with AC are characterized by facial dysmorphias, such as midface hypoplasia, a short upturned nose with anteverted nostrils, and a protruding forehead, which are not registered in patients with PSAC. Some patients with AC are diagnosed with respiratory problems after birth because of the small size of the chest and increased mobility of the costosternal joint, resulting in chest narrowing during inspiration (paradoxical

Table 2. Comparative analysis and radiological signs of achondroplasia and pseudoachondroplasia

X-ray	Achondroplasia	Pseudoachondroplasia
Skull	Enlarged size of the cranial vault with frontal, parietal, and occipital protuberances and reduced size of the base of the skull and foramen magnum	Normal X-ray presentation
Spine	Decreased inter-arch distance in the caudal direction of the lumbar spine	Biconvex shape of the vertebral bodies with anterior linguliform protrusion of the central part (in childhood)
Tubular bones	Shortening and thickening of the tubular bones, moderate metaphyseal changes, more in the distal femur and proximal tibia, and normal ossification of the epiphyses, except for a slow process in the knee joint, and the fibula is longer than the tibia	Shortening of the tubular bones with markedly expanded, irregular metaphyses, and small deformed epiphyses
Hip joints	Square shape of the iliac wing, horizontal acetabulum and narrow sciatic notches, radiolucency of the proximal femur in infancy; ectrosyndactylia	Small, round, indistinct epiphyses of the femur in pediatric patients, uneven ossification of the acetabular hood, and severe dysplastic coxarthrosis in adults
Hands	Short proximal and middle phalanges, divergence of fingers II, III, and IV (ectrosyndactylia), and short metacarpals	Short phalange, short metacarpals with cone-shaped epiphyses, and scyphoid metaphyses (ball-in-socket)

respiration). In addition, hydrocephalus and stenosis of the foramen magnum are relatively common in patients with AC, which may necessitate neurosurgical correction. In contrast to AC, patients with PSAC have joint damage, accompanied by severe joint hypermobility and arthralgia since early childhood.

However, despite some phenotypic differences in patients with AC and PSAC, the analysis of X-ray examination data is essential in differential diagnostics at the clinical level. Table 2 presents a comparative analysis of the radiological signs of patients with AC and PSAC.

Thus, the analysis of X-ray examination data of the skeleton, especially the long bones, hip joints, and hands, in patients with AC and PSAC revealed significant differences, and its use will optimize the differential diagnostics.

As in the vast majority of patients with AC, in our sample, 98% of patients had a major *FGFR3* mutation c.1138G>A (p. Gly380Arg) or c.1138G>C (p. Gly380Arg). As in previous studies of patients with PSAC, the common mutation c.1417_1419del (p. Asp473del) was revealed in *COMP* as responsible for the disease onset, which was registered in 27% of patients with PSAC.

DISCUSSION

AC and PSAC are skeletal dysplasias with similar phenotypic manifestations and different etiopathogenetic mechanisms. Numerous studies have established that *FGFR3* mutations responsible for AC belong to the activating class (gain-of-function), causing the activity of the fibroblast growth factor receptor. Increased transduction of intracellular signaling pathways, including STAT1 and MAPK, significantly suppresses the proliferation and maturation of growth plate chondrocytes and, as a result, inhibits longitudinal bone growth [21, 22]. Another signaling pathway, initiated by the C-type natriuretic peptide (CNP), modulates FGFR3 activation, which underlies the recently proposed therapy of AC with a CNP analog (vosoritide) to improve the growth rates of patients with AC [23].

The protein product of *COMP* as responsible for PSAC development is significant in the organization of the extracellular matrix and is expressed in the cartilage tissue, tendons, and ligaments, which explains their defect in PSAC [11, 12]. Most *COMP* mutations disrupt the amino acid sequence of T3 repeats that bind calcium ions, which is necessary for the proper folding and secretion of protein into the extracellular matrix [24]. This leads to its accumulation in the cisternae of the rough endoplasmic reticulum, which induces cellular stress and apoptosis of chondrocytes and ultimately slows down the ossification and growth of tubular bones [25–27].

The common clinical manifestations of these two diseases include disproportionate dwarfism, rhizomelic limb shortening, brachydactyly, joint hypermobility, lower limb deformity, and moderate muscular hypotension. Despite the significant similarity of the clinical manifestations of these two diseases, several phenotypic characteristics enable us to distinguish these diseases from each other. Thus, in patients with AC, macrocrania, protruding frontal eminence, a saddle nose bridge, and midface hypoplasia are noted, which are not typical for PSAC [1, 3]. In addition, specific X-ray signs of PSAC, such as a pronounced decrease in the size and deformity of the epiphyses, and the characteristic shape of the vertebrae are detected on radiographs in the lateral projection, and rounded epiphyses and scyphoid metaphyses of the metacarpal bones (ball-in-socket) are also registered [18, 28]. When conducting differential diagnostics, anamnestic data must be considered. An analysis of the history of the patients and literature data suggests that the first signs of disproportionate dwarfism in AC occur from birth or even in the prenatal period, whereas in PSAC, a decrease in height and rhizomelic limb shortening become apparent only after the age of 1 year.

A certain difficulty in the differential diagnostics of AC and PSAC is attributed to the polymorphism of the clinical manifestations of PSAC, including in members of the same family. We have attempted to conduct clinical and genetic correlations in patients with PSAC. Nucleotide variants were predominantly localized in exons 13 and 9 of *COMP*. Moreover, 7 patients (27%) had a frequent deletion of the GAC repeat c.1417_1419del (p. Asp473del) in exon 13. Since this deletion can be evaluated separately by Sanger sequencing, several authors propose to analyze it as the first line of PSAC diagnostics [29]. In the analysis of the clinical manifestations in these patients aged 3–18 years, the phenotype, as a rule, corresponded to a severe form of PSAC with growth retardation from –3.75 SD to –10.62 SD, except for one family case, when, in contrast to the severe phenotype in the mother, the 11-year-old daughter had mild PSAC manifestations, moderate valgus deformity of the knee joints, and growth deficit of –3.21 SD. Interfamilial clinical polymorphism was also registered in two probands with PSAC, caused by a missense mutation in exon 9, previously described in a patient with severe PSAC, c.925G>C (p. Gly309Arg) [30]. In our sample, a 4-year-old girl had moderate clinical manifestations (height –0.25 SD), whereas a 16-year-old boy had severe clinical manifestations (height –6.22 SD). The mild PSAC phenotype in two proband girls aged 1 and 2 years with a height of –0.66 SD and –0.96 SD, respectively, was caused by amino acid substitutions of aspartic acid at position 437, c.1309G>T (p. Asp437Tyr) and c.1309G>C (p. Asp437His).

Thus, a study of the clinical, genetic, and radiological characteristics of Russian patients with AC and PSAC and an analysis of literature data revealed a significant similarity in the phenotypic manifestations of skeletal dysplasia

in the form of disproportionate dwarfism due to rhizomelic limb shortening, brachydactyly, interphalangeal joint hypermobility along with limited elbow joint extension, and varus deformity of the lower extremities. Such specific clinical manifestations make it difficult to differentiate AC from PSAC. However, a more thorough analysis of their phenotypic characteristics and X-ray examination findings enables us to increase the efficiency of their differentiation at the clinical level and optimize molecular–genetic diagnostics. Considering the peculiarities of the etiology of these two diseases, in particular the presence of a major *FGFR3* mutation responsible for 97% of AC cases and the existence of a significant polymorphism of the clinical manifestations of PSAC, in which severe clinical manifestations similar to those in AC occur, a diagnostic search from major mutation analysis is encouraged. In the absence of this *FGFR3* mutation, the next stage of the molecular–genetic study may be the analysis of a frequent *COMP* mutation, a deletion of the GAC repeat in exon 13. This mutation was detected in 16%–30% of patients with PSAC described in the literature and in 27% of the patients in our sample [19, 20]. In the absence of these two mutations, a targeted gene panel or complete exome sequencing is necessary to clarify the diagnosis.

CONCLUSION

Following a comprehensive study of the phenotypic characteristics and radiological changes in the skeleton of patients with AC and PSAC, in conjunction with the analysis of literature data, the differential diagnostic criteria for these diseases were clarified. The use of these criteria by practicing physicians who consult patients with skeletal pathology will help optimize the planning for DNA diagnostics, reducing the economic and time costs for its implementation.

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Author contributions. *T.V. Markova* and *V.M. Kenis* developed the study design, reviewed the literature, and wrote and edited the text of the article. *T.S. Nagornova, N.N. Vasserman, N.Yu. Ogorodova,* and *O.A. Shchagina* performed laboratory molecular–genetic diagnostics, analyzed the study results, and wrote the text of the article. *E.V. Melchenko, D.A. Reshchikov, A.E. Alieva, D.V. Osipova,* and *L.A. Bessonova* collected and processed the clinical material and analyzed the data obtained. *E.L. Dadali* developed the study concept and edited the article text.

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