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Case Report

A Novel Homozygous Variant in the COMP Gene Causing a Multiple Epiphyseal Dysplasia 1 with Autosomal Recessive Inheritance

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Abstract: Multiple epiphyseal dysplasia type 1 is one of the most common autosomal dominant types of the genetically heterogeneous group of skeletal dysplasias characterized by impaired ossification of the epiphyses of long bones. To date, it is known that the disease is caused by heterozygous variants in the *COMP* gene and is characterized by a significant variability in the clinical manifestations. We report the first case of a patient with MED 1 caused by novel homozygous single nucleotide variant c.2170dupG (p.Val724Glyfs*20) in the *COMP* gene identified by whole-exome sequencing. The following segregation analysis in the family found a detected variant in heterozygous state in healthy consanguineous parents of the proband. Clinical and radiological examination revealed the atypical signs of epiphyseal dysplasia including limited range of extension and supination of both forearms, severe bilateral ulnar clubhand, plano-valgus deformity of the feet and generalized muscle weakness with gait disturbances. Among the clinical features, myopathic signs were the most prominent. The radiological and neurophysiological data can be helpful in the differential diagnostics with the congenital myopathies. The novel homozygous variant in the *COMP* gene that caused multiple epiphyseal dysplasia 1 with autosomal recessive inheritance can contribute to the more detailed description of genotype–phenotype correlations, which will allow research to understand better the role of the C-terminal domain of COMP.

Keywords: *COMP*; multiple epiphyseal dysplasia; myopathy

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1. Introduction

Multiple epiphyseal dysplasia type 1 (MED 1) (OMIM:132400) is one of the most common autosomal dominant types of the genetically heterogeneous and clinically variable group of skeletal dysplasias characterized by impaired ossification of the epiphyses of long bones [1]. The disease is caused by heterozygous variants in the *COMP* gene located on chromosome 19p13.1 [2]. The protein product expressed by the gene is a pentameric glycoprotein of the thrombospondin family which plays an important role in matrix organization and endochondral ossification through catalyzing polymerization of collagen fibrils and forming a macromolecular protein network via its interaction with collagen types I, II, IX, XII, XIV, matrilin-3, aggrecan, fibronectin and integrin [3–6]. Clinical presentation of MED 1 varies widely and can modify as the disease progresses. The onset of the symptoms occurs by the ages of 2–3 and includes waddling gait, muscle weakness, difficulty climbing stairs and getting up from the floor [7]. These symptoms develop mostly as a result of impaired formation of the epiphyses of long bones and ligamentous laxity of the joints;

however, in the majority of the patients myopathic symptoms are misdiagnosed in early childhood [8]. Moderate elevation of creatine phosphokinase (CPK) levels noted in some patients supports the clinical findings. By the age of 5–6 years, above-mentioned symptoms are being accompanied by knee and ankle pain that leads to the suggested diagnosis of rheumatoid arthritis in some of those patients [1]. As a result, in many cases the diagnosis of MED 1 can be confirmed in adolescence only, mostly after X-ray examination for the suggested diagnosis of arthritis. Typical radiographic features of MED 1 include abnormal size, shape and structure of the epiphyses which are described as their fragmentation, irregularity and flattening [1,9]. Osteoarthritis of the hip and knee joints progresses rapidly and can lead to total joint replacement surgery at a relatively young age [10].

To date, all identified cases of MED 1 are inherited in an autosomal dominant manner and are caused by heterozygous pathogenic variants in the *COMP* gene.

We report the first case of a patient with MED 1 caused by novel homozygous duplication c.2170dupG (p.Val724Glyfs*20) in the *COMP* gene.

2. Materials and Methods

We observed a 12-year-old patient with clinical and radiographic features of MED 1. To confirm the diagnosis, the following methods were used: genealogical analysis, clinical examination, neurological examination with psycho-emotional testing, radiography, magnetic resonance imaging (MRI), electroneuromyography (EMG) and evaluation of plasma CPK levels. Molecular Genetic Confirmation of the Diagnosis was based on the results of whole-exome sequencing.

Whole exome sequencing (WES) was performed on Illumina NovaSeq 6000 instrument (Illumina, San Diego, CA, USA) using the SureSelect Human All Exon V7 target sequences enrichment system (Agilent Technologies, Santa Clara, CA, USA) in 2 × 100 bp paired-end mode. The average coverage of the patient's complete exome was ×77.7; the breadth of coverage ≥×10—96.05%. The method of selective capture of DNA regions belonging to the coding regions of about 20,000 genes was used for sample preparation. To indicate the revealed variants, the nomenclature presented on the website http://varnomen.hgvs.org/recommendations/DNA (accessed on 10 May 2022), version 2.15.11 was used. The sequencing data were processed using in-house pipeline. 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 [11–13].

To assess the clinical relevance of the identified variants, the OMIM database and the HGMD® Professional pathogenic variants database version 2019.4 were used [14,15]. 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 [16].

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 (Thermo Fisher Scientific, Waltham, MA, USA). The primer sequences were selected according to the reference sequence of the target regions of the *COMP* gene (NM_000095.3).

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the Research Center for Medical Genetics, Moscow, Russia (protocol code 2021-3, 12 March 2021). Proband's parents gave informed consent to the genetic testing and the publication of their child's anonymized data.

3. Results

The proband is a 12-year-old girl with complaints of progressive gait disturbances, poor tolerance of physical activities, inability to squat and get up from squatting position without support (Govers' sign), hip and ankle pain when walking, elbow and wrist joints contractures and feet deformities.

The parents of the proband are fourth cousins of Russian ancestry; both parents are healthy. The father's height is 182 cm, and the mother's height is 164 cm. The proband has an 8-year-old healthy brother.

The girl was from the first pregnancy, complicated by an oligohydramnios and anemia in the mother. The birth weight was 3200 g, the birth length was 51 cm and the girl had Apgar score 8/9. Psychomotor development was normal; she has been holding her head from the age of 3 months, sitting since the age of 6 months, independent walking from the age of 1 year and active speech from 1.5 years. From early childhood, gait disturbances and poor motivation to participate in the active games were noted. At the age of 3 years, inability to get up from squatting position without support was noticed. At the age of 7 years, muscle weakness and fatigue when walking increased, the child had difficulties climbing stairs and getting up from the floor without support, gait disturbances progressed. At the same time, a contracture of the right elbow joint was noted occasionally during the physical education classes. The MRI of the right elbow joint revealed notching of the humeral condyle. Further examination of the proband revealed generalized joint laxity and bilateral plano-valgus deformity of the feet. At the age of 9 years, limited range of motion in the wrist joint and complaints of weakness and pain in the upper and lower limbs appeared. At the age of only 10 years, the child underwent the complete radiological examination of the spine and joints and the diagnosis of MED was supposed. Given the signs of proximal muscle weakness and suspected myopathy, it was decided to delay further orthopedic management until the results of neurological and genetic examinations.

On examination at the age of 12 years, the height was 146 cm (−1.30 SD), weight was 32 kg (−1.93 SD), which corresponded to average physical development and no signs of body disproportion were noted (Figure 1).

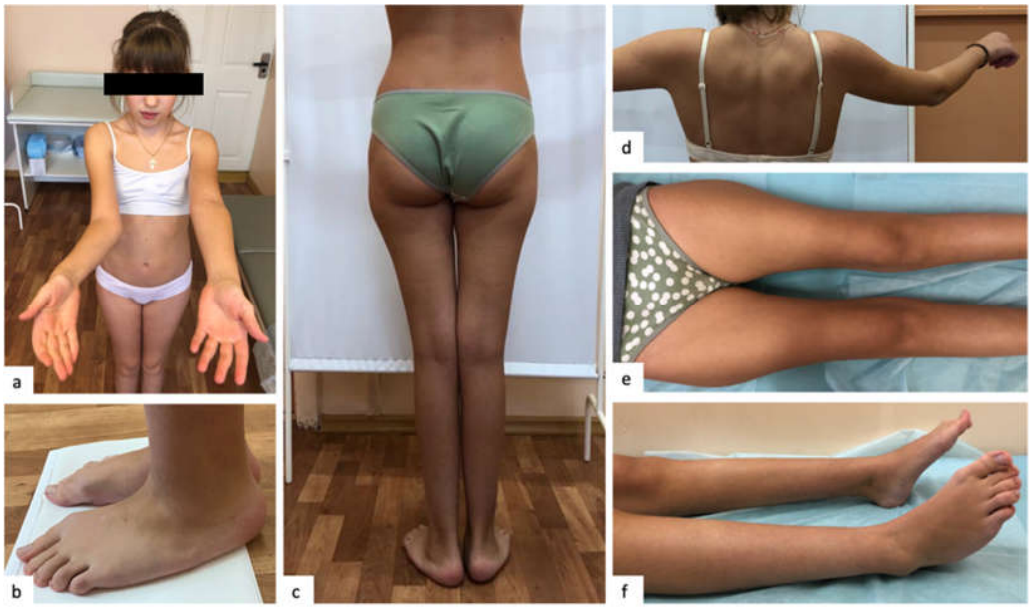

Figure 1. Patient's general appearance at the age of 10 and 12 years. (**a**,**d**) The contracture of the right elbow joint; (**b**) Plano-valgus deformity of the feet; (**c**,**e**,**f**) leg muscles hypotrophy.

Orthopedic examination revealed flexion contracture in the right elbow and excessive pronation of both forearms along with hypermobility in the interphalangeal joints; the right upper limb was shorter than the left due to a flexion contracture. Supination of the forearms was limited and painful. Ulnar deviation (ulnar clubhand) on both sides was revealed. There was no remarkable spinal deformity, but the range of flexion-extension and rotational movements of the spine was mildly limited. The axis of the lower extremities was moderately valgus, the patellas were centered and relatively high positioned (patella alta) and the rotation of the hip joints was moderately painful in extreme positions. Torsional

deformity of the lower extremities was found, excessive internal rotation of the hips with limited external rotation and external torsion of the tibia (left 60°, right 40° with normative value of 10–20°). Flexible plano-valgus deformity of the feet.

The neurological examination revealed hypotrophy of the shoulder girdle and leg muscles, atrophy of the wrist and thigh muscles and hypotonia of the limb muscles. Reduced strength of the shoulder and pelvic girdle muscle (4/4), the wrist muscles (3/2) and the anterior thigh muscles (3/3) were noted. The girl could not get up from a squatting position without support. Gait was similar to the Trendelenburg gait. Tendon reflexes were symmetric and normal, there were no pathological signs and sensation was intact.

Examination of the child's parents did not reveal any signs of skeletal dysplasia and neurological pathology.

Radiographic examination of the proband revealed the signs of epiphyseal dysplasia that appeared by decreased height and abnormal shape of the epiphyses, valgus deformity of the lower extremities. The most pronounced and unusual changes were found in the distal forearms and wrists. Severe hypoplasia and deformity of the distal ulna, accompanied by secondary deformity of the distal radius and dislocation of the carpal bones were noted. Remarkable radiographic signs of plano-valgus deformity of the feet (decrease in the arch height) accompanied by abnormal shape of the tarsal bones were noted (Figure 2).

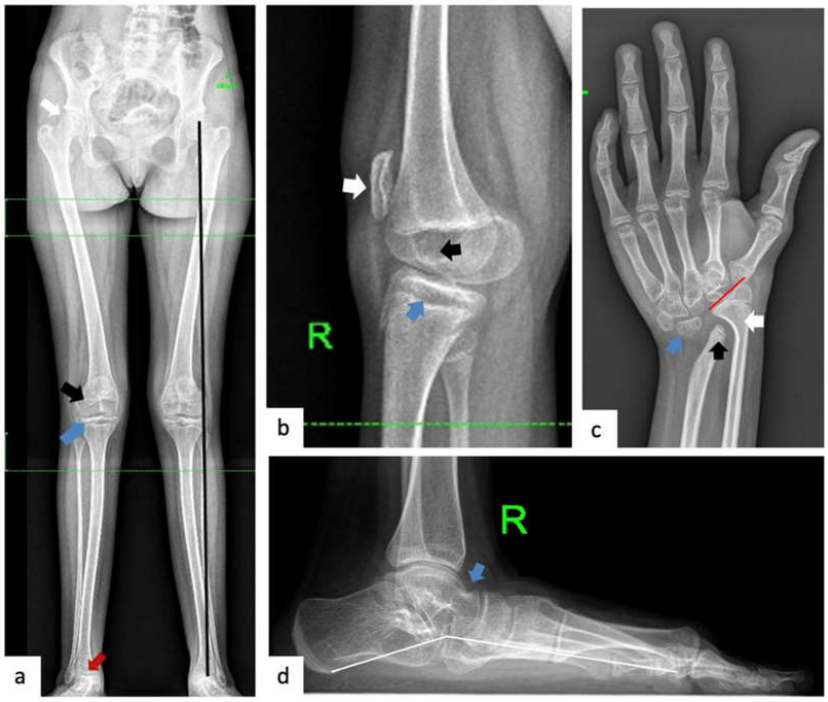

Figure 2. (**a**) Anteroposterior standing radiograph of the lower extremities: valgus deformity (lateral deviation of the mechanical axis of the lower extremities—black line); flattening and deformity of the femoral head (white arrow); flattening of the distal epiphysis of the femur and shallow intercondylar notch (black arrow); decreased height and flattening of the intercondylar eminence of the proximal tibial epiphysis (blue arrow); reduced height and wedge-shaped deformity of the distal tibial epiphysis, valgus deformity of the ankle joint (red arrow); (**b**) Lateral radiograph of the knee joint: decreased height of the distal femoral epiphysis (black arrow); decreased height of the proximal tibial epiphysis (blue arrow); high position and decreased size of the patella (patella alta) secondary to decreased height of the epiphyses (white arrow); (**c**) Anteroposterior radiograph of the wrist and hand: hypoplastic distal ulna (black arrow); deformity of the distal radius (white arrow); ulnar sloping of the articular surface of the radius (red line); dislocation of the carpal bones (blue arrow); (**d**) Lateral standing radiograph of the foot: decreased height of the foot arch (the arch angle is indicated by white lines); deformity of the talus—shortening of the neck—and deformity of the head (blue arrow).

The level of CPK was within normal ranges (96.5 U/l). Needle EMG was performed twice, at the ages of 7 and 12 years. Both studies showed changes in the leg muscles which are typical for primary neuromuscular diseases without spontaneous activity. The motor unit action potentials duration was slightly reduced; however, there was an increased number of polyphasic motor unit action potentials up to 40–50%. Both studies demonstrated signs of the myogenic pattern without spontaneous activity.

At the age of 12 years, an MRI of the leg muscles was performed (Figure 3). Reduced volume of the anterior compartment of the thigh and lower leg muscles was noted. No other muscle changes were seen on T1-weighted images. T2-weighted short-tau inversion recovery (STIR) imaging showed hyperintense signal in the quadriceps and gastrocnemius muscles bilaterally.

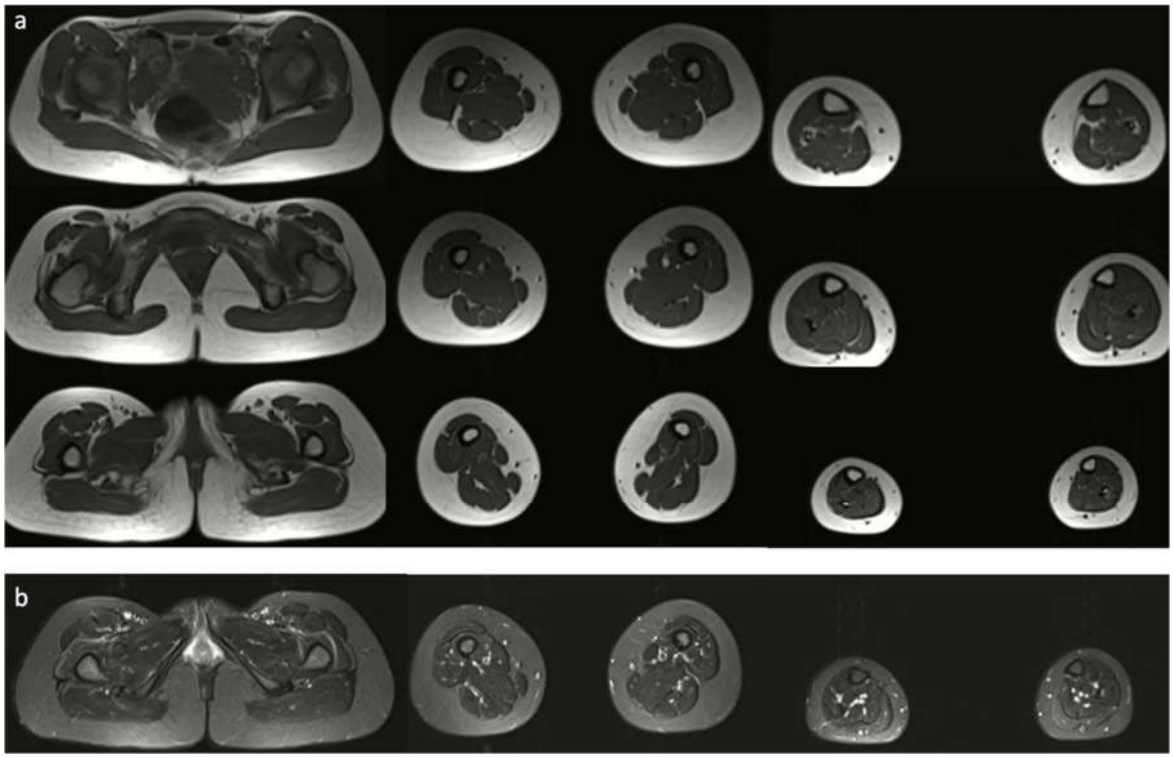

Figure 3. T1-weighted (**a**) and T2-STIR (**b**) muscle MR-images of the lower limbs. Reducing the volume of the anterior compartment of the thigh and lower leg muscles is noted. There is no moth-eaten appearance on T1-weighted images (**a**). T2-STIR images (**b**) show no edematous changes of quadriceps and gastrocnemius muscles.

Based on clinical, radiological and neurophysiological data, the diagnosis of MED 1 with myopathy was suspected. The whole-exome sequencing revealed a novel homozygous single nucleotide duplication in exon 18 of the *COMP* gene (NM_000095.3): c.2170dupG resulting in a frameshift starting from codon 724 (p.Val724Glyfs*20). The identified variant is absent in the gnomAD database and affects the highly conserved position of the protein product of the *COMP* gene [13]. Based on the above-mentioned data, the identified variant is classified as a variant of uncertain significance, according to international recommendations for the interpretation of data obtained by massive parallel sequencing [16]. The segregation analysis by the automated Sanger sequencing revealed the variant in the heterozygous state in both parents (Figure 4).

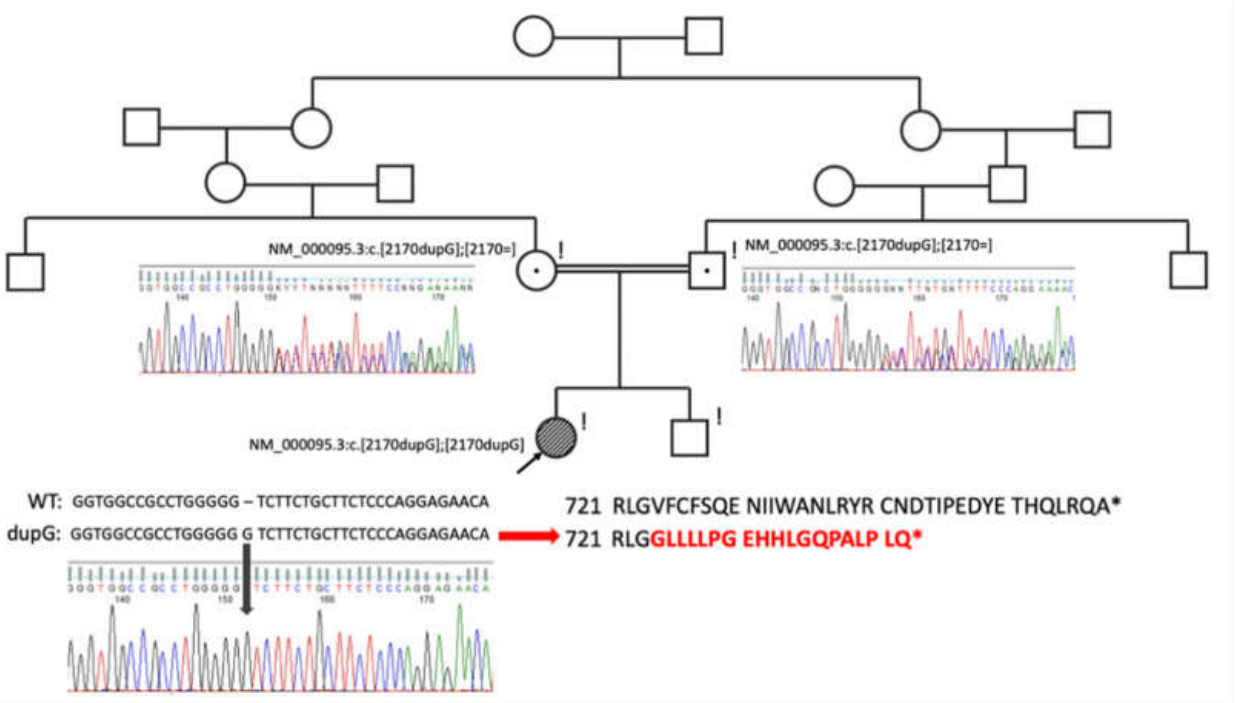

Figure 4. A novel homozygous frameshift variant that disrupts the sequence of 35 amino acid residues in the C-terminal domain of the COMP: c.2170dupG (p.Val724Glyfs*20) was identified in the proband. Segregation analysis of this variant in the family confirmed its presence in the heterozygous state in the parents.

4. Discussion

MED 1 is an autosomal dominant skeletal dysplasia caused by pathogenic variants in the *COMP* gene, which is characterized by a generalized change of the epiphyses of the long bones leading to the early osteoarthritis of the large joints. Bony and ligamentous changes can be accompanied by symptoms of mild myopathy in some cases [17]. The protein product of the *COMP* gene is expressed in cartilage, ligaments and tendons and plays an important role in extracellular matrix organization [18]. To date, 74 variants in the *COMP* gene associated with MED 1 are described according to HGMD professional database, most of which being missense substitutions localized in 8–14 exons of the gene coding calmodulin-like protein domain repeats [2,15]. Significantly less often, single nucleotide variants leading to changes of the amino acid sequence of the C-terminal globular domain are found [19]. Most of the identified variants in the *COMP* gene affect the formation of the protein tertiary structure and disrupt its interactions with other proteins, particularly type IX collagen and matrilin-3, in the cisterns of the rough endoplasmic reticulum, causing cellular dysfunction, endoplasmic reticulum stress and chondrocyte apoptosis [20–22].

MED 1 is characterized by a significant variability in the clinical manifestations, and its diagnosis can be challenging due to atypical clinical and radiological features, as well as the inter-familial and intra-familial phenotypic variability [23]. The first pathogenic variants in the *COMP* gene were identified more than 25 years ago; however, clear genotype–phenotype correlation has not yet been obtained. We report the case of a 12-year-old girl with MED 1 caused by novel homozygous duplication c.2170dupG resulting in a frameshift starting from codon 724 (p.Val724Glyfs*20) in the *COMP* gene identified by whole-exome sequencing.

Analysis of the clinical manifestations of MED in our patient revealed some atypical features of the disease course. The patient's height was within normal ranges (-1.3 SD) and no disproportion between the limbs and the trunk was detected, which indicates a mild MED phenotype. The classical presentation of MED includes the pain in the hip, knee

and/or ankle joints after physical activity. The progress of the disease leads to the development of early osteoarthritis, especially in the large joints of the lower extremities [1,24,25]. The patient presented in the current report had complaints of waddling gait and poor tolerance to long-distance walking, but the initial manifestation of the disease which led to the suspicion of the primary skeletal condition was the contracture of the right elbow joint without history of previous trauma. Surprisingly, the first suspicion was made by the physical education teacher. With the growth of the patient, the radiological picture of epiphyseal dysplasia characterized by the changes of the shape and structure of the epiphyses of the long bones became more noticeable. However, the radiological features were not compatible with those typical for MED caused by pathogenic variants in the *COMP* gene (characteristic pattern of impaired ossification and small size of the epiphyses were not detected). While involvement of the proximal joints (hips and knees) is more typical for MED, the most striking clinical and radiological findings in the proband were noted in the distal joints (wrists, ankles and hindfoot joints). The pattern of deformity of the wrist joints with severe ulnar hypoplasia accompanied by ulnar clubhand and dislocation of the carpal bones seems to be characteristic for this patient with MED associated with homozygous variant in the *COMP* gene.

The identified homozygous variant in the *COMP* gene, c.2170dupG (p.Val724fs*20), is a nucleotide duplication close to the 3′-end of the transcript that leads to a change in the polypeptide chain in the C-terminal region of the protein, which is 35 amino acid residues long. Segregation analysis of this variant in the family confirmed its presence in the heterozygous state in consanguineous parents who did not show any signs of the disease. Pathogenic nucleotide variants that disrupt amino acid sequences in the C-terminal region are rarely registered in patients with MED 1. So, Mabuchi A. et al. in 2003 described a familial case of MED 1 caused by the variant c.2223dupC (p.Asn742Glnfs*2) found in exon 18 of the *COMP* gene with the 3′-terminal localization, that, as well as in the present case, belongs to the class of duplication with a frameshift, but in the heterozygous state [26]. The authors suggested that the identified variant leads to considerably truncated protein (15 amino acids shorter), and the phenotypic effect of this variant manifests as a mild form of MED with normal stature (-1 SD) and with involvement of the hip and knee joints.

To the best of our knowledge, only one familial case of MED 1 with a homozygous variant has been previously described; compound heterozygous variants have not been described. A homozygous missense variant in exon 13 of the *COMP* gene: c.1423G > A (p.Asp475Asn) was identified by Tariq M. et al. in 2018 in a large consanguineous Pakistani family with a severe form of PSACH in two individuals; another 14 family members presented with a mild PSACH or MED 1 phenotype [27]. The authors suggested the first model of dose-dependent inheritance of the *COMP* gene variant, when homo- and heterozygous forms correlated with the degree of growth retardation and the severity of skeletal damage in family members.

The identified variant c.2170dupG (p.Val724Glyfs*20), as well as the previously described c.2223dupC (p.Asn742Glnfs*2) variant, lead to a protein truncating by 15 amino acids; however, it is remarkable that heterozygous carriers of the identified variant do not show any clinical signs of MED. In contrast to the previously described variant c.2223dupC (p.Asn742Glnfs*2), the variant c.2170dupG (Val724Glyfs*20) leads to a substitution of 19 amino acid residues, resulting in the formation of a premature stop codon. Biallelic loss-of-function variants in *COMP* gene has not been previously described as a possible cause of the development of a hereditary disease, and according to the work of Svensson et al., 2002, COMP-deficient mice (COMP-null mice) did not have any phenotypic features [28]. This suggests that the identified variant leads to a weaker gain-of-function effect, in contrast to the previously described pathogenic variants. Consequently, we did not find any clinical symptoms of MED 1 in the parents of the proband, who were heterozygous carriers of the identified variant. However, there are no homozygous loss-of-function variants in the gnomAD population database. Therefore, we do not exclude that the mechanism of the disease in our proband may be associated with a biallelic loss-of-function due to a

change in the COMP stability. Further studies are needed to explain the pathogenesis of the moderate clinical manifestations in patients with MED 1 caused by c.2170dupG (p.Val724Glyfs*20) variant.

Our patient showed atypical disease progression with the signs of proximal muscle weakness and suspected myopathy. Needle EMG and muscle MRI revealed minor abnormalities, which did not allow us to exclude or confirm the diagnosis of a primary muscle disease. Symptoms of moderate myopathy have been described in a number of patients with MED 1 caused by pathogenic variants in the *COMP* gene, most often found in the C-terminal region of the protein [17,29]. The studies by Pirog K.A. et al. on knockout mouse models for the p.Thr585Met variant in the C-terminal domain showed that muscle weakness occurs primarily due to the pathology of the myotendinous junction and is associated with the perimysium surrounding the bundles of muscle fibers and responsible for the force transmission from muscles to tendons [30]. The abnormal organization of collagen fibrils discovered by the authors led to the thinning and weakening of tendons. In addition, there was a significantly increased number of fibers with central nuclei in the myotendinous junction. Thus, it was concluded that the symptoms of myopathy are the result of tendons pathology. The patient we observed was diagnosed with myopathic symptoms much earlier than MED was confirmed. It should be noted that some patients with MED 1 are misdiagnosed with myopathies and get long-lasting observation by a neurologist. The present case will contribute to a better understanding of the differential diagnoses between some variants of MED 1 and primary neuromuscular diseases.

Therefore, we have identified a novel homozygous frameshift variant that disrupts the sequence of 35 amino acid residues in the C-terminal domain of the COMP: c.2170dupG (p.Val724Glyfs*20), which expands the spectrum of pathogenic variants in the *COMP* gene causing the MED phenotype. In addition, the features of the disease course in our patient can contribute to a more detailed description of genotype–phenotype correlations, which will allow research to fully understand the important role of the C-terminal domain of COMP.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the Research Center for Medical Genetics, Moscow, Russia (protocol code 2021-3, 12 March 2021).

Informed Consent Statement: All patients involved in the study gave written informed consent to the clinical examination and publication of their anonymized data.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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