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CASE REPORT

# Phenotypical reflection of a patient with a possible pathological variation of the vcp gene and difficulties in neuromuscular differential diagnosis

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ABSTRACT

The differential diagnosis of muscle weakness includes a wide spectrum of diseases, from cerebrovascular diseases to motor neuron diseases, peripheral neuropathies, neuromuscular junction diseases and myopathies. Although many methods are used to make a diagnosis, including anamnesis, examination, laboratory, electrophysiological examinations, radiological examinations, biopsy and genetic analysis, there are still many patients who cannot be diagnosed. In this article, we present a case in which it was not possible to differentiate between inclusion body myopathy, amyotrophic lateral sclerosis and hereditary motor neuropathy. A 59-year-old male patient presented with chronic progressive muscle weakness and myalgias. The patient, who had complaints for approximately 8-9 years, had a family history supporting an autosomal dominant inheritance pattern. In the patient's neurological examination, muscle weakness affecting the distal and proximal parts of the bilateral lower and upper extremities, atrophy in the thenar and hypothenar regions of the upper extremity, and hypoactive deep tendon reflexes were detected. Other neurological examinations were normal. Laboratory tests revealed no pathology other than moderate CK elevation. Electrophysiological findings supporting the association of motor neuropathy and myopathy were detected in electromyography. No pathology was detected in muscle biopsy other than mild inflammatory changes. Genetic examination of the patient revealed a heterozygous mutation (c.365C>G protein Thr122Arg) in the T122R variant of the Valosin-containing protein (VCP) gene. When the literature is reviewed, although there are some variants of VCP gene mutations associated with familial inclusion body myopathy, amyotrophic lateral sclerosis accompanied by frontotemporal dementia, and Charcot-Marie-Tooth (CMT) 2Y, this variant in our patient has not been described before. The patient's family history of autosomal dominant trait and the presence of both IBM and CMT clinics suggest that these two clinics are phenotypically reflected together as a secondary to the current mutation. In this period when genetic treatments are rapidly developing, it is of great importance to identify genetic muscle diseases and new variants, so such cases should be reported. In patients whom differential diagnosis cannot be made, advanced genetic examinations should be performed even if genetic examinations such as NGS are found negative.

Keywords: VCP mutation, motor neuron disease, inclusion body myositis, hereditary polyneuropathy.

## INTRODUCTION

The etiology of muscle weakness may not be determined even if many methods are used. When genetic studies such as next-generation sequencing are also inadequate, whole exon sequencing should be used as the last step for diagnosis. With this method, we detected a new possible pathogenic variation in the valosin-containing protein (VCP) gene in a patient with muscle weakness. Among the 241 VCP variants identified to date, 102 have been classified as likely pathogenic or pathogenic [1]. The clinical manifestations of these defined variations are in three main forms: inclusion body myositis (IBM) and Paget disease, Charcot-Marie-Tooth (CMT) 2Y and amyotrophic lateral sclerosis

(ALS) and frontotemporal dementia (FTD) complex [2-5]. In the patient we described, all these clinics are observed together with the new variation.

## CASE REPORT

A 59-year-old male patient presented to our neurology clinic with quadriparesis. His first complaints were back pain and widespread muscle pain that started 5-6 years ago. Over time, numbness and tingling in the fingers and quadriplegic weakness, more severe in the lower extremities, developed in all extremities. He had difficulty climbing stairs and began to fall frequently. There was no known disease in his medical history. He had been using gabapentin for 2 years due to neuropathic pain. There was a 35 pack/year smoking history. When his family history was examined, it was learned that his mother, brother and sister also had a similar history of weakness.

In his neurological examination, bilateral thigh flexion and extension were 3-4/5, left knee flexion and extension were 3/5, right knee extension was 2/5 flexion was 3/5, right foot dorsiflexion was 1/5 plantar flexion was 3/5, left foot dorsiflexion and plantar flexion was 3-4/5, bilateral handgrip was 2-3/5, bilateral elbow flexion was 3/5, elbow extension was 4/5, bilateral shoulder abduction and adduction was 4/5. There was bilateral, asymmetric, and distally dominant muscle weakness. There was muscle atrophy in all four extremities. There were no pathological reflexes or clonus. Deep tendon reflexes could be obtained in the upper extremities, but not in the lower extremities. There were no autonomic symptoms. Pes cavus and hammertoe deformities were present. He could walk with only one support. There were fasciculations in the arms. There was difficulty swallowing solid foods.

In his examinations, hemogram, routine biochemistry, rheumatological markers, HbA1c, brucella, syphilis, thyroid functions, vitamin B12, folic acid, sedimentation, peripheral blood smear, serum protein electrophoresis were found to be normal. Creatine kinase (CK) level was detected as 323 U/L. No significant pathology was detected in complete urine analysis.

Sensory nerves were found to be normal in electromyography (EMG). Motor responses in the median and ulnar nerves could not be obtained

| RIGHT | LEFT | Muscle | Maximal Contraction | Submaximal contraction | | Spontaneous activity | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Duration | Polyphasia | Fb | PSW | |
| | * | M.INTER OSSE DORS 1 | severe reduce | ↑ | N | - | - | |
| | * | M.ABD.POLL.BREVIS | no voluntary activity | | | 3+ | 3+ | |
| | * | M.ABD.DIG.MINIMI | | N,myogenic | ↑ | - | - | |
| * | | M.INTER OSSE DORS 1 | mild reduce | N,↑ | N | 3+ | 3+ | pseudomyotonia |
| | * | M.TIB.ANT. | submaximal | N | N | 1+ | 1+ | |
| | * | M.RECTUS FEMORIS | severe reduce | N,myogenic | ↑ | - | - | |
| | * | M.TRAPEZIUS | | N | N | - | - | |

| RIGHT | LEFT | Examined Nerve | Conduction velocity m/sec | Distal conduction latency miliseconds | Distance mm | Amplitude |
|---|---|---|---|---|---|---|
| | * | **N.MEDIANUS (S)** | 45 | 2,4 | | 32µV |
| | * | **N.ULNARIS (S)** | 44 | 3,2 | | 32µV |
| | * | **N.SURALIS (S)** | 42 | 3,2 | | 8µV |
| | * | **N.MEDIANUS (Mt)** | NO RESPONSE | | | mV |
| | * | **N.ULNARIS (Mt)** | NO RESPONSE | | | mV |
| | * | **N.FIBULARIS (Mt)** | 43 | 4,4 | | 6-5mV |

**Figure 1.** EMG findings. N: nervus, M: musculus, Fb: fibrillation, PSW: positive sharp waves, S: sensorial, Mt: motor, m/sec: meters/second, mV: milivolts, µV: microvolts, mm: milimeters, ↑: increased

on the left. Fibular nerve motor compound muscle action potential (CMAP) conduction velocity and amplitude were normal. Denervation potentials, more neurogenic motor unit potentials (MUP) in the distal and more myogenic motor unit potentials (MUP) in the proximal, and loss of MUP were observed in needle EMG (Figure 1).

Cranial and cervical magnetic resonance imaging showed no findings other than mild cerebral atrophy.

Muscle biopsy was performed for differential diagnosis of myopathy (Figure 2). Histopathological findings were interpreted as not supporting the presence of myopathy.

The pedigree was established by the medical genetics polyclinic and was evaluated as autosomal dominant (OD) inheritance pattern (Figure 3).

In order to make a genetic diagnosis for the patient, "whole exome sequencing" (WES) was performed. As a result of the analysis, the c.365C>G change in the 4th exon of the VCP gene was detected as heterozygous. This change was not reported in the Clinvar database (1) and was classified as a likely pathogenic change according to the American College of Medical Genetics and Genomics (ACMG) criteria [6].

Pathogenic alterations in the VCP gene have been associated with autosomal dominant inheritance of early-onset Paget disease and inclusion body myopathy with frontotemporal dementia 1 (IBMPFD-1) (Multisystem proteinopathy) (OMIM#167320), autosomal dominant inheritance of frontotemporal dementia and/or amyotrophic lateral sclerosis 6 (OMIM#613954), and autosomal dominant inheritance of Charcot Marie Tooth disease type 2Y (OMIM#616687) [7].

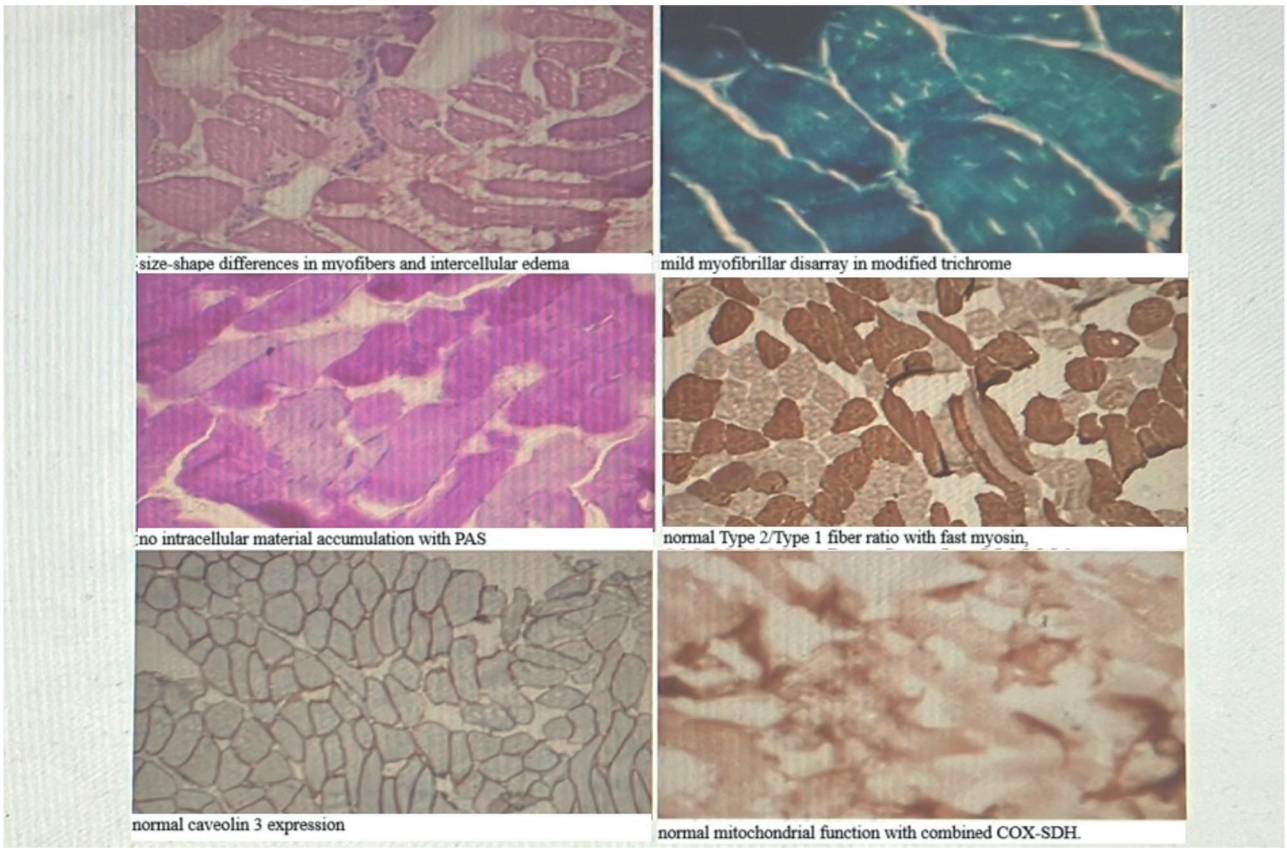


**Figure 2.** Muscle biopsy images: Microscopic findings showed no signs of muscle injury other than size-shape differences in myofibers and intercellular edema. There was no increase in interstitial tissue in Masson trichrome. There was no obvious pathology except mild myofibrillar disarray in modified trichrome and NADH-TR. There was no Myophosphorylase enzyme was normal in controlled repeat stainings (McArdle disease was excluded). There was no intracellular material accumulation with Oil red O and PAS, and no amyloidosis with crystal violet.. In immunohistochemical staining, sarcolemmal dystrophin, sarcoglycans (A, B, D, G), dysferlin, caveolin 3, cytoplasmic calpain 3 and collagen 6 expression were normal. With fast myosin, Type 2/Type 1 fiber ratio and distribution were normal. There were no pathological immature fibers with neonatal myosin. No inflammatory cells were detected with LCA, CD3, CD20, CD68. Pathological diagnosis resulted as striated muscle tissue showing nonspecific changes.

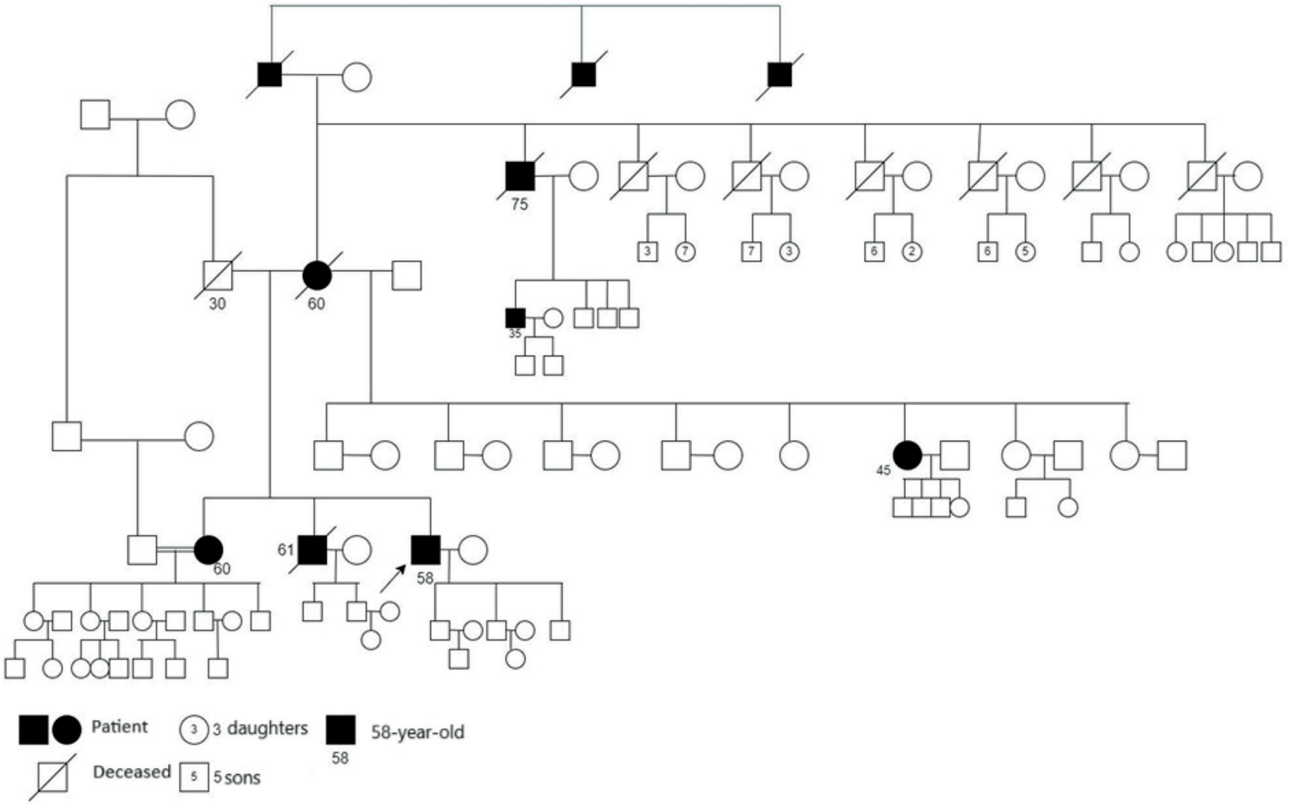


**Figure 3.** Pedigree

Since frontotemporal dementia can also be seen in this gene positivity, cognitive evaluation was performed.

Standardized Mini Mental Test Score: 10/25 (Subtests that could not be evaluated due to the patient not being able to use both hands were not included in the scoring). The score was observed below normal limits. In the subgroup scoring, the patient lost the most points from recording, attention and delayed recall. (Orientation: 6/10, Record: 1/3, Attention: 1/5, Delayed Recall: 0/3, Language: 2/4).

No lytic lesions or hardening of bone tissue supporting Paget's disease were observed in the knee tomography.

The patient was started on riluzole treatment. No worsening of swallowing difficulty was observed at the 2-year follow-up examination. Previously he was able to walk with a single cane, but now he could walk with a double cane. In muscle strength examination, there was distal and proximal tetraparesis, more dominant in the distal. Atrophy was observed in bilateral thenar and hypothenar muscles. In the deep tendon reflex examination, the biceps could not be obtained on the right and was hypoactive on the left, and reflexes could not be obtained in the lower extremities. Hoffman was bilaterally negative, and plantar skin response was bilaterally flexor.

## DISCUSSION

The most important feature of this case report is the description of a previously unidentified variation in the VCP gene that causes a severe syndromic presentation including autosomal dominant myositis, hereditary motor predominant polyneuropathy and motor neuron disease clinics. It is also emphasized that next-generation sequencing alone is not sufficient to overcome the difficulties in differential diagnosis in hereditary forms of neuromuscular diseases, and whole exon sequencing has an important place.

In the family we described, the index case's CK elevation, proximal muscle weakness, significant myogenic MUP changes in the proximal muscles on EMG, and the size-shape difference in myofibers and intercellular edema detected on muscle biopsy can be interpreted in favor of myopathy, while the patient's complaints started with numbness-

tingling in the fingers of four extremities, the absence of deep tendon reflexes despite no apparent atrophy in the early stages, the presence of pes cavus and hammertoe deformities on the feet, and the widespread decrease in the CMAP amplitudes of the motor nerves on nerve conduction study on EMG while the observation of neurogenic MUP changes in the distal areas on needle EMG can be interpreted in favor of polyneuropathy. In addition to the patient's neurogenic MUPs, the detection of denervation potentials in the cervical and lumbar segments, changes in motor amplitudes, and dementia findings with obvious attention deficits could not exclude the motor neuron disease frontotemporal dementia complex. For these reasons, the patient's diagnosis could not be fully established until WES was performed.

The VCP gene is located on chromosome 9. It is a protein that has important roles in chromatin organization, membrane fusion, ubiquitin-dependent protein degradation and autophagy. VCP is a protein that is a member of the AAA+ (diverse activity-associated ATPase) protein family. It exhibits multifunctional properties and expresses in every tissue. Although the exact role of VCP in skeletal muscle is not yet known, VCP mutations lead to the accumulation of ubiquitinated inclusions and protein aggregates in patient tissues, transgenic animal models and in vitro systems [8]. One study found that VCP was localized intranuclearly in differentiated skeletal muscle tissue [9]. VCP has been found to be widespread in the sarcoplasm of skeletal muscle, and also in the perinuclear region and within endomysial vessels [10,11]. In cultured myotubes, VCP is mostly found in the cytoplasm [12]. This may suggest that VCP changes its localization and perhaps its function depending on the differentiation status of the cells.

There are many variations identified in the VCP gene. Paget disease, inclusion body myositis, FTD and ALS complex and CMT2Y diseases have been reported to develop as a result of these variations [2-5].

The most common general features of patients diagnosed with IBMFTD are proximal muscle weakness, which causes morbidity as in our index case, in approximately 90%, Paget disease in 51%, and FTD-type dementia in 32%. Sensory motor axonal neuropathy has rarely been described in these patients. Although muscle biopsies may show vacuoles in some patients, more commonly ubiquitinated sarcoplasmic and myonuclear inclusions associated with VCP and TDP-43 inclusions are observed [2]. However, slight changes can also be detected, as in our patient.

Pathogenic variants in the VCP gene have been newly associated with CMT type 2. A family with a new associated variant (VCP (p.S171R)) was identified. Mild sensory symptoms and findings characterized by chronic progressive motor axonal loss on repeated EMGs were observed in this family [3]. In the case we describe, sensory complaints, hypoactive or absent DTRs on neurological examination, decreased motor amplitudes on EMG, and neurogenic changes in distal muscles on needle EMG suggest that the patient's clinical picture resembles the CMT2Y phenotype.

In a recent study, it was observed that protein aggregates accumulated secondary to mutated SOD1 interact with VCP protein in motor neurons derived from pluripotent stem cells obtained from an ALS patient with SOD1 mutation, and SOD1 toxicity was reduced when VCP was overexpressed. Changes in VCP homeostasis have been highlighted as one of the main factors that may cause faster degeneration in diseased motor neurons [4]. Another study described familial ALS due to VCP mutation [13]. Considering this feature of VCP, it is understandable that ALS could not be excluded in the patient we described. Finally, studies emphasize that VCP mutations can cause the FTD phenotype. Recently, VCP mutations have been shown to lead to abnormal accumulation of enlarged endosomes and lysosomes, as well as to reduce autophagy flux and increase tau phosphorylation. It has been emphasized that tau hyperphosphorylation on these pathways also causes FTD type dementia [5].

The C.-365C>G variant that we identified in our patient was searched in the literature and in databases where genetic variations are stored, but it was determined that it has not yet been identified. It can be said that this variant is a more severe form that phenotypically includes both IBM, CMT2Y and ALS-FTD clinics, based on the patient and family history we reported. However, further studies are required to demonstrate which pathways and cellular dysfunctions are responsible for the clinical manifestation of this variant.

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**Conflict of interest**

The authors declare that there is no conflict of interest.

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