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RESEARCH ARTICLE

Charcot Marie Tooth Disease type 2 caused by the R191Q Mutation in the *Valosin-Containing Protein* gene

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ABSTRACT

VCP-MSP (valosin-containing protein causing multisystem proteinopathy) is an uncommon autosomal dominant disorder caused by mutations in the *Valosin-containing protein* (*VCP*) gene. It has been reported in diverse populations worldwide and the common phenotypes are inclusion body myopathy, Paget's disease of bone and frontotemporal dementia. We present a patient of Asian Indian descent with a rarely reported phenotype of neuropathy, Charcot-Marie-Tooth disease type 2 caused by the R191Q mutation. Our report expands the phenotype that can be associated with this specific mutation and confirms the worldwide distribution of VCP-MSP.

Keywords: *Valosin-containing protein (VCP)* gene, inclusion body myopathy, Paget's disease of bone, frontotemporal dementia, Charcot-Marie-Tooth disease type 2.

Introduction

The *Valosin-containing protein (VCP)* gene encodes an ATPase which is involved in multiple cellular processes. Mutations in this gene can result in an autosomal dominant multisystem disorder. The tissue affected can include muscles, inclusion body myopathy (IBM), bone, Paget's disease of bone (PDB) and/or brain, frontotemporal dementia (FTD). In the original description of the genetics of this disorder, the condition was called inclusion body myopathy associated with Paget's disease of bone and frontotemporal dementia (IBMPFD)[1]. However more recently, it has been designated VCP causing multisystem proteinopathy (VCP-MSP)[2]. Although myopathy is the most common feature of VCP-MSP, other rare phenotypes including Charcot-Marie-Tooth disease type 2 (CMT2) have been reported[3]. Advent of whole exome sequencing has made it possible to identify the rare genetic mutations, however there is no clear genotype- phenotype correlation in patients with *VCP* gene mutations.

We describe a patient of north Indian descent characterized by an unusual phenotype and a mutation in the *VCP* gene not previously described in this distinct ethnic group.

Case report

This is a 49-year-old right-handed man who presented for a neuromuscular second opinion for complaints of distal weakness in his legs. This developed about two years earlier and was associated with complaints of numbness in his feet. He saw a neurologist and based on his history, clinical examination and electromyography (EMG) testing; he was diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP). He was treated with intravenous immunoglobulin (IVIG) with a dose of 2 g/kg infused over five days per month for more than two years. While on this treatment his condition progressed, and he started to have frequent falls and weakness in his arms.

His neurological review of systems was otherwise negative, and his medical history was unremarkable. In addition, he had no symptoms of memory loss or changes in cognitive function. The patient is gainfully employed in a position that requires significant cognitive capacity, and he has not noticed any deficits in terms of his ability to perform his job.

Neurological examination showed a normal mental status and cranial nerve examination. He had generalized hyporeflexia +1 at the biceps, triceps, brachioradialis with unobtainable patellar reflexes or ankle jerks and flexor plantar responses. Sensory examination showed normal proprioception at the great toes bilaterally with an equivocal decrease in vibration in a stocking distribution worse distally. Pinprick sensibility was reduced in a stocking distribution worse distally in his feet. Cerebellar tests were normal. Power testing showed Medical Research Council (MRC) grade 4/5 weakness of both deltoids, supraspinatus and infraspinatus and 5-/5 weakness of the biceps muscles. Mild weakness was present in the small hand muscles testing the adductor digiti minimi, first dorsal interosseous and abductor pollicis brevis (5-/5). Wrist flexion and extension as well as the triceps were 5/5. In his legs he had 4/5 weakness of hip flexion, knee flexion, foot eversion, inversion and dorsiflexion bilaterally. Hip abduction and adduction strength were preserved 5/5. He could not walk on his heels or toes and had a significantly positive Romberg sign.

The follow investigations were done to identify the cause of his neuropathy and were normal or negative: thyroid studies, complete blood count and differential, blood urea nitrogen and creatinine, comprehensive metabolic panel (including an alkaline phosphatase), creatine phosphokinase and aldolase, serum protein electrophoresis and immunofixation, serum vascular endothelial growth factor, serum B12 and folate, serology for hepatitis C, human immunodeficiency virus, human T-lymphotropic virus 1, human T-lymphotropic virus type 2 and Lyme disease, antiganglioside panel including anti-GM1/ anti-MAG antibodies, hemoglobin A1c levels, a 2-hour glucose tolerance test and erythrocyte sedimentation rate.

The patient is an immigrant from northern India and his father died of throat cancer in his sixties. His mother, age 77 years, was diagnosed with Parkinson's disease and prior to that had a stroke. He has two brothers and two sisters. One sister passed away and had been diagnosed with dementia beginning at age 60 years and another brother suffered a stroke. He has three daughters and one son who are all healthy. There is a history of consanguinity as his parents were distant second cousins. No one else has any neurological conditions to suggest neuropathy, myopathy, multiple sclerosis, or muscular dystrophy. No further information is available regarding the health status of his grandparents. The EMG was repeated, and the results of the nerve conductions studies are indicated in Table 1.

Table 1. Nerve conduction studies

Nerve	Distal latencies, ms (normal values)	Response amplitude, mV	Conduction velocity, m/s	F-wave latency, ms	Comments
Motor					
Right Median	**4.8** (<4.2)	**7.2** (>4.0)	**46** (>50)	**35** (<30)	
Left Median	**5.2** (<4.2)	**7.1** (>4.0)	50 (>50)	**38** (<30)	
Left Ulnar	**4.3** (<3.3)	**3.6** (>3.5) **1.4** (BE) (>3.5) **1.0** (AE) (>3.5)	**30** (>50) **21**(>50)	**38** (<30)	
Bilateral Peroneal	**NR** (<6.2)	**NR** (>2.6)	**NR** (>40)	**NR**	No response recording the extensor digitorum brevis
Bilateral Tibial	**NR** (<6.0)	**NR** (>4.0)	**NR** (>40)	**NR**	
Sensory					
Bilateral Sural	**NR**				
Bilateral Peroneal	**NR**				
Left Median		**10.2** (>20 µV)	**38** (>50)		
Left Ulnar		**2.7** (>17 µV)	50 (<50)		
Left Radial		**5.0** (>15 µV)	**44** (>50)		

NR-no response ; AE-above elbow; BE-below elbow

Since the results of the previous study were available, a comparison of the two studies showed similar values in both motor and sensory nerve conduction parameters. In both studies the presence of ongoing denervation in form of positive sharp waves and fibrillation potentials in the weak muscles was observed. However, in the prior study large motor units with increased amplitude and duration were noted. In our study, in addition to these changes, a high proportion of low amplitude polyphasic motor units suggesting elements of ongoing motor unit regeneration. In our study, significant features of demyelination such as prolonged distal latencies, slowed motor conduction velocities, temporal

dispersion or conduction block were not found. Based on our EMG testing, our overall diagnostic impression was that this patient did not have CIDP but rather axonal neuropathy. This diagnosis is further supported by his lack of response to IVIG treatment[4].

Since the routine studies performed as part of the investigation of the cause of his neuropathy were unrevealing, genetic etiology was considered. Genetic testing was performed commercially with whole exome sequencing of a panel of more than eighty genes known to cause neuropathy. A mutation was found in exon 5 of *VCP* gene, rs121909334, p.Arg191Gln (R191Q), c.572G>A (NM_007126.3). Interestingly the R191Q mutation had been reported as disease producing first published in 2004 by Watts et al[1] in the original description of the genetic basis of IBMPFD. In our patient, this mutation is the cause of his neuropathy representing a form of Charcot-Marie-Tooth disease.

Discussion

The *VCP* gene encodes the valosin-containing protein which is expressed in multiple tissues and often at very high levels representing up to 1% of cytoplasmic proteins. This protein mediates multiple cellular processes that can include the ubiquitin-proteasome system, membrane fusion, cell cycle control, regulation of autophagy and protein quality control[2]. Clinically, more than 90% of patients develop inclusion body myopathy, 40% Paget's disease of bone and 30% frontotemporal dementia[5]. These disorders may or may not exist in the same individuals and there is significant intrafamilial clinical variability. Atypical phenotypes reported include Alzheimer's disease (2%), Parkinson's disease (4%), and amyotrophic lateral sclerosis in up to 10% of patients. Rarer neurological conditions that have been reported as case reports include spastic paraparesis, sensory neuropathy and the diagnosis observed in our patient, CMT[2].

The first description of a *VCP* gene mutation causing CMT was reported in 2014, the p.Glu185Lys mutation. This was an American family with variable age of onset of symptoms[5] and designated CMT Type 2 (CMT2). Next, in 2015, a case of CMT2 was reported in a 62-year-old American man, with history and examination consistent with a sensorimotor neuropathy[6]. Electrophysiology testing revealed a neuropathy with axonal features and genetic testing revealed a p.Gly97Glu mutation confirming a genetic neuropathy. Our patient represents the third case of CMT2.

The mutation carried by our patient, p.Arg191Gln, was first described in the publication describing IBMPFD. This was a family in which the phenotype was amyotrophic lateral sclerosis without IBM, FTD or Paget's disease[1]. This mutation was also reported in a European patient with Paget's disease with no other manifestation of the disorder[7] indicating interfamilial variability. Then in 2018, two families with combined five members from the United States were reported with p.Arg191Gln all of them suffering IBM and two with associated PDB and two with FTD[8].

Our patient's mother has Parkinson's disease and since this is an autosomal dominant disorder, she likely carries the same mutation causing a different phenotype. In addition, it is also possible that the patient's sister, who died with a diagnosis of dementia, also carried the same mutation with a different phenotype. This variation in neurological phenotype is consistent with the intrafamilial variation observed in families carrying mutations in the *VCP* gene[5]. However, since they are not available for further study, their genotype cannot be confirmed.

VCP-MSP is a rare disorder and as of 2022, only 50 mutations have reported[7,9]. Although it has a worldwide distribution, there are few reports from patients originating in the Indian subcontinent[7]. In terms of this specific mutation, previous patients carrying the R191Q mutation are from the United States and Europe. Since it is not likely that our patient is related to those reported from other countries, we suggest that these mutations arose independently in these populations. This may indicate that this DNA site is a relative hotspot prone to spontaneous mutation.

At the present time, there is no specific treatment that is available to treat this disorder[9]. In 2021, a Cure VCP scientific conference was held supported by non-profit organizations and attended by patients, families, basic science researchers and clinicians[10]. In the near future, it is anticipated that clinical trials will be initiated testing a variety of proposed therapies. It is important to note that any therapeutic intervention will require confirmation of diagnosis by genetic testing. An additional benefit of genetic testing is that it would facilitate genetic counseling of families and at-risk children. Furthermore, although no treatment is available at this time, genetic testing would enable the option of pre-implantation genetic diagnosis allowing the testing of at risk embryos and transfer of those that do not carry a pathogenic mutation. This process would ensure that children of affected parents would be unaffected and prevent transmission to future generations[11].

Conclusion

Our study expands the spectrum of VCP-MSP phenotype associated with the R191Q mutation to include CMT2, and further expands the distribution to include patients in the Indian subcontinent. A genetic diagnosis is important as demonstrated in our patient and allows physicians to avoid expensive treatments such as IVIG. In addition, it allows for genetic counseling and hopefully, future research into the development of a specific therapy for VCP-MSP.

Conflicts of Interest Statement:

The authors have no conflict of interest to declare.

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