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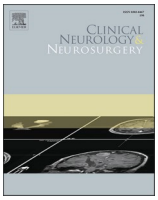

Sex influences clinical phenotype in valosin-containing protein mutations: A case family report and systematic literature review

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ABSTRACT

Objective: Mutations in the valosin-containing protein (VCP) gene cause autosomal dominant multisystem proteinopathy 1 (MSP1), characterized by a variable combination of inclusion body myopathy (IBM), Paget's disease of bone (PDB), and frontotemporal dementia (FTD). Here we report a novel *VCP* missense mutations in an Italian family with FTD as the prevalent manifestation and compare our results with those described in the literature.
Methods: We described the clinical, molecular, and imaging data of the studied family. We also conducted a systematic literature search with the aim of comparing our findings with previously reported *VCP*-related phenotypes.
Results: A novel heterozygous *VCP* missense mutation (c 0.473 T > C/p.Met158Thr) was found in all the affected family members. The proband is a 69-year-old man affected by progressive muscle weakness since the age of 49. Muscle MRI showed patchy fatty infiltration in most muscles, and STIR sequences revealed an unusual signal increase in distal leg muscles. At age 65, he presented a cognitive disorder suggestive of behavioral variant FTD. A bone scintigraphy also revealed PDB. The patient's mother, his maternal aunt and her daughter had died following a history of cognitive deterioration consistent with FTD; the mother also had PDB. No relatives had any muscular impairments. Reviewing the literature data, we observed a different sex distribution of *VCP*-related phenotypes, being FTD prevalence higher among women as compared to men (51.2 % vs 31.2 %) and IBM prevalence higher among men as compared to women (92.1 % vs 72.8 %).
Discussion: This study broadened our clinical, genetic, and imaging knowledge of *VCP*-related disorders.

1. Introduction

Heterozygous missense mutations in valosin-containing protein (*VCP)* gene cause a rare autosomal dominant, adult-onset, progressive disorder, characterized by inclusion body myopathy (IBM) associated with Paget's disease of bone (PDB) and frontotemporal dementia (FTD), also called multisystem proteinopathy 1 (MSP1) [1,2]. Rarely, atypical manifestations including amyotrophic lateral sclerosis (ALS), neuropathy, parkinsonism, and ataxia may occur [3].

VCP encodes a multifunctional protein that acts as a molecular chaperone involved in proteolysis, intracellular membrane fusion, cell cycle regulation, and autophagy [4]. To date, more than 50 heterozygous missense mutations in *VCP* have been identified without a clear genotype-phenotype correlation and with a widespread intra and inter-family clinical variability [3]. Myopathy is the first and the main clinical manifestation, being present in almost 90 % of cases; PDB is diagnosed in half MSP1 population, while FTD is observed in about 30 % of patients, usually in advanced stages of the disease [2,5,6]. FTD without muscle symptoms has only been found in less than 5 % of the cases, with or without PDB [6]. In patients with MSP1, a higher

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incidence of FTD among women as compared to men has been suspected [5]. A recent study reported a high rate of *VCP* mutated patients — mostly women — from 5 families presenting FTD without muscle involvement [7]. Here we report a novel heterozygous missense mutation in exon 5 of *VCP* in an Italian family in which FTD was the predominant clinical manifestation. Three of the four members, all women, were affected by FTD with no muscle impairment. We then reviewed all the cases with *VCP*-related FTD cases described in the literature in order to test the hypothesis of a higher FTD prevalence among females in *VCP*-mutated people.

2. Case presentation

Patient III:1 (Fig. 1), the proband, is a 69-year-old man who, at the age of 49, began to experience a progressive upper girdle weakness, subsequently involving facial and lower limbs muscles. At the age of 61, in another Institution, he had undergone a genetic test for facioscapulohumeral muscular dystrophy, with negative result, and a muscle biopsy of the vastus lateralis which had showed muscle fiber caliber inhomogeneity and hypotrophy, and nuclear internalizations (Fig. 2, A-C). Since the age of 65 he also exhibited progressive cognitive impairment and behavioral disturbances. At first neurological examination at our Institution, he showed axial muscle weakness with asymmetric scapular winging and difficulty in the transition from the sitting to the standing position; walking was possible only with support. No muscle or bone pain was reported. Blood tests showed slightly increased CK levels (295 U/L) and quantitative EMG examination, performed in the right and left vastus lateralis, tibialis anterior, soleus, biceps brachii, and deltoid muscles, documented mixed myopathic and neuropathic changes, without spontaneous activity. Motor and sensory nerve conduction studies of the tibial, peroneal, ulnar, and median nerves, were unremarkable. Muscle MRI revealed diffuse atrophy and fatty infiltration that, in some muscles, had a patchy distribution (Fig. 2, D-H); the vastus lateralis muscle, where the biopsy had been taken, also showed marked fatty infiltration. The STIR scan showed increased signal intensity in leg muscles (Fig. 2, I).

The neuropsychological examination, which included global measurements (Mini-Mental State Examination), Digit and Visuo-spatial Span forward, Rey Auditory Verbal Learning Test, Trail Making Test A, attentional matrices, language and phonemic fluency task, constructional praxis (Rey-Osterrieth complex figure copy, Clock test), and executive function tests (Trail Making test B, Stroop Test, and Frontal Assessment Battery) [8], revealed a moderate language impairment, and attention and executive dysfunctions. Behavioral changes such as apathy, loss of empathy, compulsive behavior, and loss of insight were also detected. Brain MRI was normal, while brain FDG-PET showed bilateral fronto-temporal hypometabolism (Fig. 3, A). Amyloid-PET showed no β-amyloid deposition. A diagnosis of behavioral variant FTD (bvFTD) was entertained [9]. Having received written informed consent, we performed targeted resequencing of 241 associated with inherited neuromuscular disorders using next-generation sequencing as reported [10]. We identified a heterozygous missense mutation c 0.473 T > C/p.Met158Thr in the *VCP* gene. The variant was validated by PCR-based standard capillary Sanger sequencing. No mutations were detected in genes associated with dementia including microtubule associated protein tau (*MAPT*), progranulin (*GRN*), amyloid-beta precursor protein (*APP*), and presenilin (*PSEN*) 1 and 2 genes. Similarly, we did not detect pathological repeat expansions in the chromosome 9 open reading frame 72 (*C9orf72)*. Apolipoprotein E (APOE) haplotype was E3/E3. At age 70, a bone scintigraphy was performed that revealed intense focal hyperactivity in the right hemi pelvis suggestive of asymptomatic PDB (Fig. 3, B).

Patient II:1 and patient II:2, the mother and maternal aunt of the index case, have been regularly monitored at our Neurological Clinic since late 1980s. Patient II:1 suffered from symptomatic PDB with bone pain and hearing loss since the age of 55. Five years later, she experienced marked language impairment that manifested as anomia and impaired single word comprehension, and changes in personality and apathy. Brain MRI showed diffuse cortical atrophy, particularly in temporal lobe, bilaterally. The patient received the diagnosis of "presenile dementia with prevalent temporal lobes impairment". She later became mutacic and totally dependent on activities of daily living and died at the age 72.

Patient II:2 began to experience behavioral symptoms such as disinhibition and irritability since age 55; executive dysfunctions and aphasia subsequently appeared. Brain MRI documented an enlargement of the subarachnoid sulci predominantly in the insula and temporal lobe bilaterally. There was marked functional impairment, and the clinical conditions progressively worsened until she died at age 65. Patient III:2, the maternal cousin of our index case, also suffered from progressive deterioration of cognition starting at the age of 50; she died at the age of 60. None of the aforementioned relatives of the proband manifested features of muscular impairment. All of them harbored the *APOE* E3/E3 haplotype. Postmortem DNA testing showed in II:1, II:2, and III:2 the presence of the same p.Met158Thr in *VCP*. Two other sisters of the proband's mother did not have neurological disturbances and died of unrelated conditions; none of them nor other patients' healthy relatives accepted to undergo DNA testing.

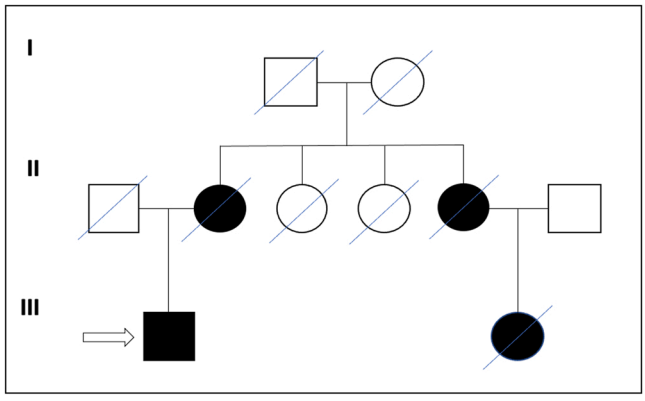

Fig. 1. Pedigree of the family. Individuals affected by MSP1 carrying the c.473 T > C/p.Met158Thr mutation are indicated with black squares (males) or circles (females). The proband is the patient III 1. The filled upper right quadrant indicates FTD, filled right lower quadrant indicates PDB, filled upper left IBM.

3. Systematic review

To compare our findings with literature data on previously described *VCP* variants, the authors (S.M., D.L., G.R.R.) independently searched the PubMed, Scopus, and Web of Science databases using "VCP", "gene", "myopathy", "multisystem proteinopathy", "FTD", and/or "dementia" as keywords. Studies were included if they describe the clinical phenotype of *VCP* variants and provide data on individual patients. Data from all the patients with *VCP* mutation were collected, with the exclusion of duplicates and cases with rare manifestations (neuropathy, amyotrophic lateral sclerosis, and parkinsonism), and grouped them according to their phenotype (FTD+IBM, FTD or IBM with or without PDB), gender, and location of *VCP* mutation. We also excluded reported familiar cases without a clear clinical, radiological, or biopsy examinations. Descriptive (mean, percentage) and statistical (Fisher's exact test and chi-squared test) were performed by using SPSS Statistics for Window.

We identified 330 VCP-related cases, 167 men and 163 woman, with a male-to-female ratio (M/F) of 1.02. Seventy-seven patients (23.3 %) had both IBM and FTD; 39 (50.6 %) were men (M/F, 1.03). In these patients, the mean age at onset was 45.7 years, with no difference between men (45.8 years) and women (44.4 years). The mutation was located in the exon 5 in 147 cases (75 %). Of the 253 *VCP* mutated

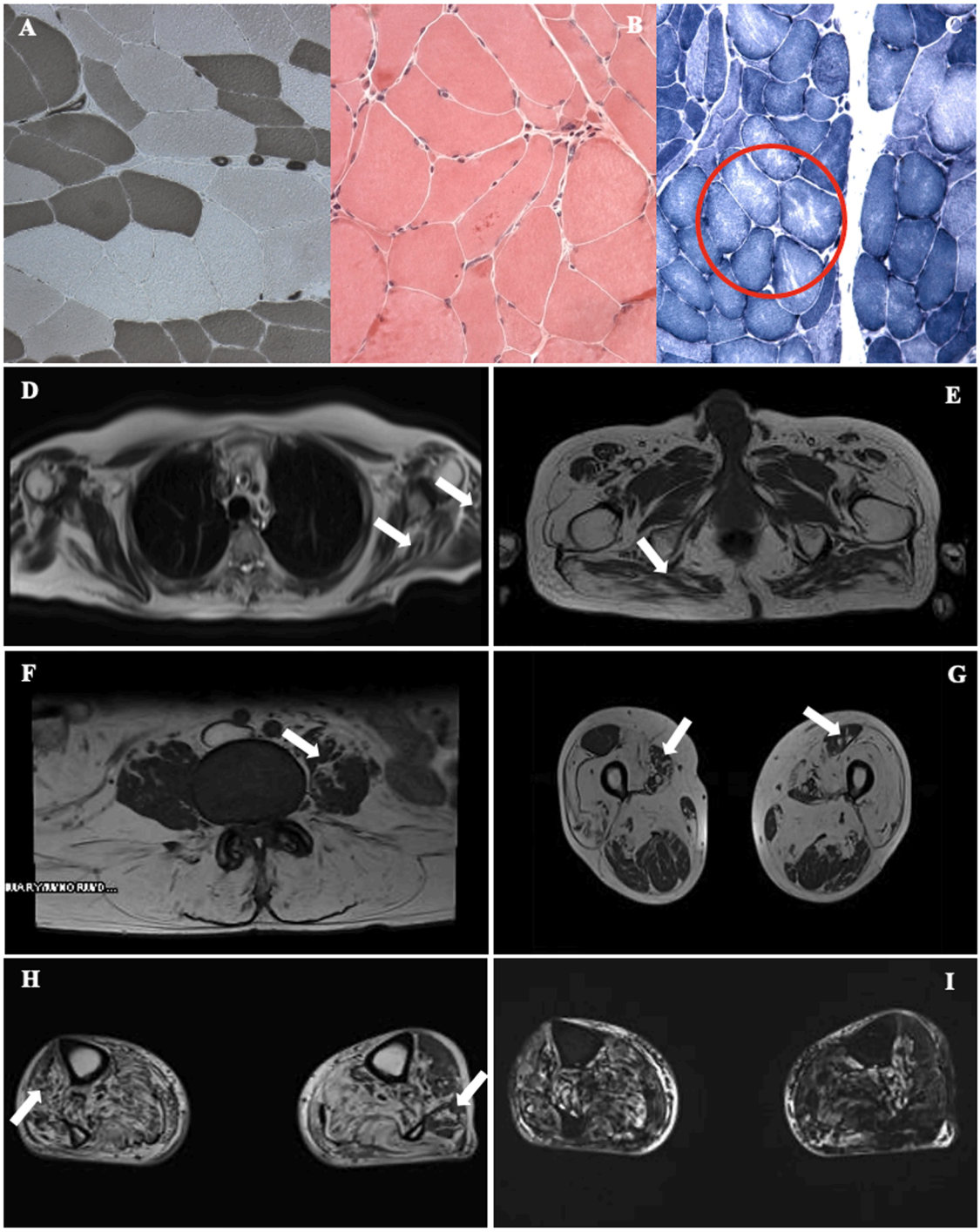

Fig. 2. Muscle biopsy of the vastus lateralis and muscle MRI: ATPase staining showing fiber types and muscular fascicle showing mild grouping(A). Fiber caliber inhomogeneity with groups of hypotrophic oblong fibers and nuclear internalizations, slight thickening of connective tissue (B). Oxidative reaction procedures reveal numerous "motheaten" fibers (circle) a sign of chronic neuropathy and myopathy degeneration (C); some fibers in regeneration; absence of sudanophil or PAS + material. No inclusion bodies could be detected. The MRI showed marked muscle fatty replacement in the muscles of the shoulder (D) and pelvic girdle (E), lumbar paravertebral spaces (F), thighs (G), legs (H), and an increased signal intensity compatible with edema in both legs, especially on the right in STIR sequence (I). Patchy infiltration, or "fat pocket" (arrows), with small areas of fat replacement surrounded by areas of normal muscle, was observed in most of the shoulder muscles, in the gluteus maximus, in the psoas, in the left rectus femoris and the right sartorius, and in tibialis anterior muscles.

patients with incomplete phenotype, 128 were men and 125 were women (M/F, 1.02).

FTD without muscle involvement was reported in 58 patients (17.5 % of all the cases) from 29 families, including our cases (Table 1). The *VCP* mutations spanned from exon 2 to exon 11, although in 44 cases (75.8 %) they were located in exon 5. The mean age at onset was 55.2 years (range, 34–75). Most cases had the behavioral variant of the disease. Forty-five of the 58 cases (77.6 %) were females (F/M ratio, 3.4). IBM without FTD was observed in 195 cases (59.1 % of all *VCP* mutated patients); 115 (59 %) were men (M/F, 1.43). The mean age at onset was 44 years. Exon 5 was the site of mutation in 76.4 % of the cases.

Overall, among the 330 *VCP* mutated cases, FTD was diagnosed in 40.9 % of the patients, affecting 50.9 % of the women, as compared to

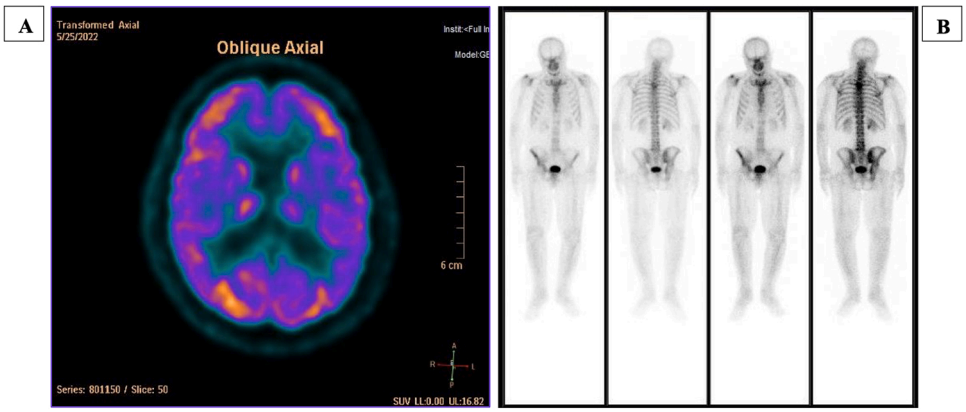

Fig. 3. Brain FDG-PET and bone scintigraphy. Brain FDG-PET (A) showed a marked hypometabolism of the anterior temporo-mesial and lateral cortices, bilaterally and a moderate hypometabolism of the orbito-frontal and medial frontal cortices. The bone scintigraphy (B) revealed intense focal hyperactivity in the right hemi pelvis suggestive of PDB.

Table 1
Summary of reported *VCP*-related FTD cases without muscle symptoms.

Amino acid change	cDNA base change	Exon	Number/ gender	Age at onset	Clinical diagnosis	n° of families	Ref.
p.Ile27Val	c.79 A>G	2	1 F/1 M	63–72	FTD	2	[24]
p.Asn91Tyr	c.271 A>T	3	1 M	66	FTD	1	[25]
p.Arg93Cys	c 0.277 C>T	3	2 F	53–59	bvFTD	1	[26]
p.Thr127Ala	c.379 A>G	4	1 F	58	bvFTD	1	[27]
p.Arg155Cys	c 0.463 C>T	5	1 F	47	svFTD	1	[16]
			1 F	-	bvFTD	1	[26]
			1 F	-	FTD	1	[1]
			1 M	-	FTD	1	[28]
p.Arg155His	c 0.464 G>A	5	3 F	-	FTD	2	[2]
p.Met158Val	c.472 A>G	5	1 M	41	svFTD	1	[29]
p.Met158Thr	c 0.473 T > C	5	3 F	50–55	bvFTD	1	(present)
p.Arg159Ser	c 0.475 C>A	5	1 F	56	bvFTD	1	[29]
p.Arg159Cys	c 0.475 C>T	5	1 F	75	FTD	1	[30]
p.Arg159His	c 0.476 G>A	5	18 F/3 M	56–71	bvFTD	5	[7]
			5 F/4 M	44–64		2	[31]
p.Ala160Thr	c 0.478 G>A	5	1 F	52	FTD	1	[17]
p.Iso206Phe	c.828 A>T	6	1 F	50	FTD	1	[32]
p.Thr262Ser	c 0.785 C>G	7	1 F	60	bvFTD	1	[30]
p.Asp387His	c.1159 A>C	10	1 F	46	FTD	1	[33]
p.Asp395Gly	c.1184 A>C	10	2 F/1 M	35–43	bvFTD	1	[34]
			1 M	45	bvFTD	1	[35]
p.Asn401Ser	c.1201 A>G	11	1 F	47	svFTD	1	[16]

FTD, frontotemporal dementia; bvFTD, behavioral variant frontotemporal dementia; svFTD, semantic variant frontotemporal dementia; -, no data reported.

31.3 % of men ($p < 0.001$) (Fig. 4, Table 2). Among the incomplete variants, FTD was diagnosed in 36 % of woman as compared to 10.1 % of men ($p < 0.001$). IBM was observed in 272 patients (82.4 % of all *VCP* mutated cases), affecting more men (92.2 %) as compared to women

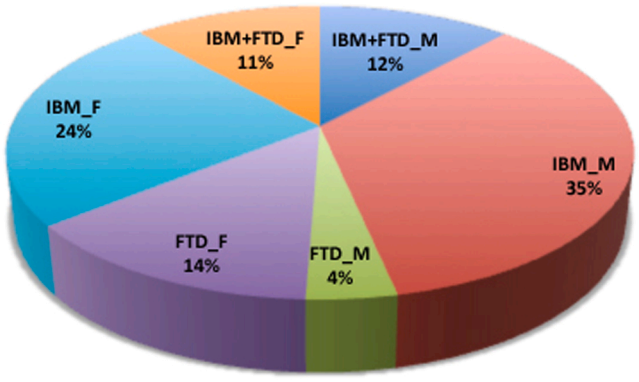

Fig. 4. Sex distribution of phenotypes among *VCP* mutated patients. IBM: inclusion body myopathy; FTD: frontotemporal dementia; M: males; F: females.

Table 2
Sex distribution of phenotypes among *VCP* mutated patients.

	Males	Females	Total	*p*
IBM+FTD	39 (11.8 %)	38 (11.5 %)	77 (23.3 %)	NS
IBM	115 (34.8 %)	80 (24.2 %)	195 (59.1 %)	<0.0001
FTD	13 (3.9 %)	45 (13.6 %)	58 (17.6 %)	0.002
Total	167	163	330	

IBM: inclusion body myopathy; FTD: frontotemporal dementia; NS: not significative. P: Chi squared test between males and females.

(72.4 %) ($p < 0.001$). Considering only incomplete variants, IBM without FTD was observed in 89.8 % of men as compared to 64 % of women ($p < 0.0001$).

4. Discussion and conclusions

We described a novel heterozygous missense mutation in *VCP*. Thus far, two substitutions at the same codon have been described, namely p. Met158Val related to ALS [11], and p.Met158Ile linked to pure IBM, or to a combined clinical picture of PDB and IBM [6,12]. The clinical

findings of our proband were suggestive for the complete triad of MSP1. Although the muscle biopsy did not present the pathognomonic inclusion bodies, muscle MRI showed the typical patchy fatty infiltration in most of the studied muscles [13]. It also revealed an unusual signal increase in the STIR sequences of the distal leg muscles, that could reflect an inflammatory process or, more probably, a certain degree of edema in the context of an ongoing muscle atrophy [14].

Of note, myopathy was detected only in the proband of our family, while FTD was present in all affected members, and it was the sole manifestation in patient II:2 and III:2. It has been proved that the presence of one or two *APOE4* alleles is associated with an increased risk of developing FTD in patients with *VCP* mutations [15]. However, all the affected family members were homozygous carrier of *APOE3*, as found in another family study [16].

Data obtained from the review of the literature confirm those previously reported [2,5,6,17] including the age at onset of IBM and FTD, and the high prevalence of mutations in exon 5. We consider our findings to be worth reporting for two reasons. First, we have shown that FTD affects a higher percentage of *VCP* mutated patients as compared to what has been previously reported [2,5,6]. It is possible that earlier studies on *VCP* mutations might have focused on IBM affected families, and more recent reports on familiar FTD cases.

Second, based on our observations and on data from the literature, it is clear that *VCP*-related FTD mainly affects women. Few studies have addressed gender differences in the epidemiological characteristics of FTD; these studies have reported a higher incidence of the disease among men [18,19]. Moreover, gender has been shown to be a potential factor in determining the phenotype of FTD, as the behavioral variant is more common in men, while primary progressive aphasia predominantly affects women [20]. Recently a higher prevalence of females has been demonstrated among FTD patients harboring *GRN* mutation [21]. Since *GRN* expression during embryogenesis plays a role in determining gender differences in the brain, it has been speculated that differences in sex hormones may influence the risk of developing *GRN*-mediated disease in a sex-dependent manner. However, *VCP,* though involved in a number of cellular processes, does not appear to be related to any sexual differentiation processes and it is not a known partner of progranulin.

On the other hand, we also observed a significantly higher incidence of IBM among men, raising the possibility that women are somehow protected against muscle involvement. Pathogenetic VCP mutations have recently been demonstrated to cause sex-specific phenotypic differences in several mutants, with higher degree of muscle impairment and respiratory chain dysfunction in males [22]. Thus, the different risk of myopathy and FTD among *VCP* mutated patients could help to better target future studies on the physiological role of VCP and on the pathogenetic mechanisms of the gene mutations.

The variable expressivity of VCP-associated disorders, with wide inter and intra-familial variations, is well known in the literature. Differences of expressivity may be related to tissue-dependent thresholds of susceptibility to the same genetic defect, especially for pleiotropic genes such as VCP. One possible hypothesis is that the location of the mutation may influence certain roles of VCP and thus lead to variation in the phenotype seen in MSP1. Patients bearing the p.Arg159Cys mutation have been found to be older at IBM onset as compared to patients with other common mutations [6]; they also do not show signs of PDB. Those cases harboring the p.Ala232Glu have an early onset of PDB and a severe phenotype [6]. Similarly, the p.Gly97Glu mutation has been associated with Charcot-Marie-Tooth disease, and the p.Arg93His reported in association with hereditary spastic paraparesis but also described in a patient with IBM [23]. Finally, inter-individual variable expressivity may reflect differences in the overall genetic background suggesting a possible role of modifying genes and/or environmental factors.

To sum up, incomplete MSP1 phenotypes are distributed differently among men and women, the latter being at higher risk of cognitive impairment regardless of type and location of the *VCP* mutation. We emphasize the importance of *VCP* genetic testing even in the absence of the full syndromic complex, especially in women with FTD not associated with more common molecular etiologies.

Ethics approval and consent to participate

The study was approved by the research ethics boards of the Careggi University Hospital (17397-oss 06/01/2021).

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CRediT authorship contribution statement

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by SM, MS, VB, DC, MB, BN, AM, FMS, AI. The first draft of the manuscript was written by DL and GRR, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare no competing interests.

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Consent for publication

Consent for publication of the current case report was obtained by the legal representative of the subject.

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