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ORIGINAL RESEARCH

Genetic Spectrum and Phenotypic Variability in Chinese Patients with Multisystem Proteinopathy and Related Disorders

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Objective: Multisystem proteinopathy (MSP) is a pleiotropic group of disorders initially presenting as inclusion body myopathy (IBM), amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and/or Paget disease of bone (PDB). Additional genes including *MATR3, OPTN*, and *ANXA11*, have recently been implicated in MSP-like disorders, further expanding the genetic spectrum. This research aims to study the genetic and clinical characteristics of MSP and related disorders in a large Chinese cohort.

Methods: Twenty-nine patients were identified in 953 patients diagnosed with ALS, IBM, or dementia at Huashan Hospital between 2000 and 2024. Variants in MSP-related genes were detected using next-generation sequencing and confirmed by Sanger sequencing. Clinical, pathological, imaging, and electromyography data were collected and analyzed.

Results: A total of 29 patients (3.0%) were identified as carrying MSP-related gene variants. Most patients were male (72.4%), with disease onset predominantly in the third to fifth decades of life. The majority of patients (21/29) presented with a single clinical phenotype. ALS was the most common phenotype (20/29), followed by IBM (10/29), FTD (7/29), and PDB (1/29). The most frequent variants were in *ANXA11* (34.5%) and *VCP* (20.7%), followed by *OPTN* (17.2%), *SQSTM1* (10.3%), *MATR3* (10.3%), and *HNRNPA1* (6.9%). All patients with *VCP* variants presented with initial lower limb involvement, whereas those carrying *ANXA11* or *OPTN* variants predominantly showed upper limb or bulbar onset. Patients harboring *OPTN* variants had a later age at onset compared with those carrying *VCP* or *MATR3* variants. Patients with ALS-onset exhibited faster progression compared with those with myopathy-onset, even when harboring identical variants.

Conclusion: This study broadens the clinical and genetic landscape of MSP and related disorders in a Chinese cohort. These results emphasize the clinical utility of next-generation sequencing for improving diagnostic accuracy in patients with unexplained neuromuscular or cognitive presentations, especially in the presence of multisystem involvement.

Keywords: multisystem proteinopathy, amyotrophic lateral sclerosis, inclusion body myopathy, neurodegeneration, ANXA11

Introduction

Multisystem proteinopathy (MSP) is a pleiotropic group disorders presenting inclusion body myopathy (IBM), amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and Paget disease of bone (PDB), which might share common pathophysiology of abnormal protein aggregates in muscle, brain, and bone.[1] MSP was first described as inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia (IBM/PFD), attributed to variants in the gene encoding valosin-containing protein (*VCP*).[2,3] Since 2013, genetic defects in *VCP* may also implicate the pathobiology of amyotrophic lateral sclerosis (ALS), providing an additional link between ALS and FTD.[4] Afterwards *HNRNPA2B1,*

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HNRNPA1, and *SQSTM1* were recognized as causative of MSPs.[4] These genes are similar to *VCP* and can both lead to multisystem involvements, affecting muscle, brain, motor neuron and bone.[5,6] Some other genes have been included under the umbrella of MSP-like disorders including *MATR3, TIA1*[7] and *OPTN*,[8] *HSPB8 and TFG*,[9] all of which are linked to a similar clinical-pathological spectrum with the combination of at least 2 of 4 manifestations (IBM, ALS, FTD, PDB). Recently, the patients who carried Annexin A11 (*ANXA11*) variants were found to present IBM and ALS/FTD, which expanded the genetic spectrum.[10]

Clinically, patients MSP typically exhibit involvement of multiple organ systems, most commonly presenting with muscle weakness, hoarseness, and dysphagia. These manifestations may occur sequentially or concurrently, and in some cases, a single predominant phenotype may persist for many years.[11] The majority of patients who present with ALS usually die from respiratory failure within 3~5 years of onset. Some patients initially presenting with muscle involvement may develop motor neuron involvement years later, accompanied by rapid disease progression. The rate of disease progression in MSP is highly variable, and effective disease-modifying therapies are currently lacking. Till now, there is no clear international consensus regarding diagnostic criteria or approved treatments for MSP. Although a standard of care has been proposed for patients with *VCP*-associated MSP, current management strategies remain largely supportive.[12] Pathologically, the presence of similar protein aggregation features across different tissues suggests a shared underlying molecular mechanism. These include dysfunction of major protein quality control pathways, particularly impairment of the ubiquitin-proteasome system (UPS) and aberrant autophagy.[13] The disparate phenotypes in muscle, brain, spinal cord, and bone are also unified by disruption of the RNA stress granule function[10,14] and accumulation of TAR DNA-binding protein 43 (TDP-43).[15,16]

At present, the disease concept and diagnostic criteria for MSP and MSP-like disorders remain incompletely defined. Recent studies have increasingly focused on MSP-like gene variants; however, most investigations have examined these variants in the context of a single clinical phenotype, such as *ANXA11* in ALS.[17,18] Several cohort studies from the United States and Japan have discussed MSP-like variants together with classical MSP genes (*VCP, HNRNPA2B1, HNRNPA1*, and *SQSTM1*), and these analyses were largely confined to specific populations.[4,19] Systematic investigations of the clinical and genetic landscape of MSP-related variants in Chinese populations are still lacking. With the widespread implementation of next-generation sequencing (NGS) in clinical practice, an increasing number of Chinese patients presenting with limb weakness, bulbar dysfunction, or cognitive impairment have undergone comprehensive genetic testing, which provide a unique opportunity to refine the disorders in a large real-world Chinese cohort.

In this study, we retrospectively analyzed a cohort of 953 patients who initially presented with ALS, IBM, or cognitive impairment and underwent genetic testing. Among them, 29 patients were identified as carrying known or novel MSP-related gene variants and exhibited characteristic MSP-associated phenotypes. More than two-thirds of these patients presented with a single clinical phenotype. ALS was the most common phenotype, followed by IBM, FTD, and PDB. The most frequently identified variants involved *ANXA11, VCP*, and *OPTN*. This study broadens the clinical and genetic landscape of the spectrum disorders in a Chinese cohort and highlights the clinical utility of NGS in improving diagnostic accuracy for patients with unexplained neuromuscular or cognitive presentation.

Methods

Study Population

Participants were inpatients or outpatients from the Department of Neurology, Huashan Hospital from 2000–2024. Twenty-nine patients who were diagnosed with MSP or MSP-like disorders were enrolled, based on the following criteria. Inclusion criteria: (1) Patients presenting with one or more MSP-related phenotypes, including IBM, PDB, ALS, and/or FTD. Myopathy was confirmed by neurological examination and characteristic features of hereditary myopathy on muscle biopsy. The diagnosis of ALS was based on progressive upper motor neuron (UMN) and lower motor neuron (LMN) dysfunction in multiple body regions, according to the El Escorial criteria.[20] FTD was diagnosed according to the Neary criteria, based on progressive behavioral and/or language impairment supported by characteristic neuroimaging findings.[21] (2) Next-generation sequencing (NGS) identified variants in genes associated with classic MSP *(VCP, HNRNPA2B1, HNRNPA1, SQSTM1)* or MSP-like disorders *(MATR3, TIA1, ANXA11, OPTN, HSPB8*, and *TFG)*.[1,4]

Exclusion criteria: (1) Patients with a clinical, histopathological, and/or genetic diagnosis of other muscular disorders, other defined motor neuron diseases, Alzheimer's disease, or secondary causes of cognitive impairment. (2) Patients without informed consent. Clinical information was collected, including natural histories of clinical symptoms, distributions of muscle weakness, serum creatine kinase (CK), imaging results, as well as bedside cognitive evaluation, for example, Montreal Cognitive Assessment (MoCA). Patients were followed every 3–6 months via telephone or in-person visits to follow up on symptom progression and survival status. All participants provided written informed consent in accordance with the Helsinki declaration, and approval was granted by the Institutional Review Board of the Huashan Hospital (KY2024-1312).

Whole-Exome Sequencing

Genomic DNA samples were extracted from peripheral blood using the QIAamp DNA Mini Kit (Qiagen). Genome sequencing libraries were prepared using the TruSeq DNA PCR-free Library Preparation Kit (Illumina) and sequenced on an Illumina HiSeq X-Ten platform (Illumina). Raw sequencing data were aligned to the human reference genome (GRCh37/hg19) and analyzed according to Genome Analysis Toolkit Best Practices recommendations. Pathogenic or likely pathogenic variant sequences were amplified with an annealing temperature predicted by DNAclub software (https://www.softpedia.com/get/Science-CAD/DNAClub.shtml). Sanger sequencing was performed to confirm the variants. Pathogenicity of each detected genomic variant was classified according to the standard guidelines.[22]

Electromyography (EMG)

Nerve conduction studies and routine EMG was performed in all subjects and by the same neurologist (Q.K). Semiquantitative evaluation of motor unit action potentials (MUAPs) was performed to distinguish neurogenic from myopathic processes. Early recruitment of short-duration, low-amplitude, polyphasic MUAPs was interpreted as a sign of myopathy. Reduced recruitment of long-duration, large-amplitude, polyphasic MUAPs was interpreted to indicate a neurogenic process. The potential for late-stage development of large -amplitude, polyphasic MUAPs in chronic myopathies was recognized, and particular emphasis was placed on analysis of MUAP duration and the recruitment pattern to distinguish chronic myopathy from a primarily neurogenic process.

Muscle Pathology

Open muscle biopsies were performed on patients with suspected myopathy. Serial frozen sections of 8 μm thickness were used for histochemical studies, including hematoxylin and eosin (H&E), modified Gomori trichrome (MGT), reduced nicotinamide adenine dinucleotide dehydrogenase-tetrazolium reductase (NADH-TR) and SQSTM1/p62 staining using the antibody of SQSTM1 (D-3) (sc-28359, Santa Cruz Biotechnology).

Statistics

Median and range were used for quantitative data such as age at diagnosis, age at onset, disease duration. Number and percentage were used for categorical data such as sex and site of weakness onset. Group comparisons were conducted using the *U*-test for two groups or Kruskal–Wallis *H*-test with Bonferroni correction for multiple groups. Kaplan–Meier curves were generated to compare the cumulative probability risk of death or mechanical ventilation between patients with ALS or myopathy onset. Gehan-Breslow-Wilcoxon test was used to determine the statistical significance in the Kaplan–Meier curves. Comparisons in categorial variable were analyzed by chi-squared or Fisher's exact tests.

$P<0.05$ was considered statistically significant. Data analysis and graphs generation were conducted using GraphPad Prism version 10.1.2 (GraphPad Software, San Diego, CA).

Results

Patient Characteristics

A total of 29 patients (Table 1) with MSP-related variants were found in 953 recorded patients with initially neurological symptoms from 2000 to 2024, including 384 patients with ALS, 431 with myopathy and 138 patients with cognitive

Table 1 Characteristics of All Genetic Tested Patients with MSP-Related Phenotypes (N=29)

Gene	Patients	Age (years)/ Sex	Age of onset (years)	Duration (months)	Sites of symptom onset	Progression (lower and/or upper limbs)	Phenotypes	Family history	Status at latest follow-up
VCP	P1	43/m	37	72	Distal LL	Lower	IBM	Yes	Alive
	P2	53/m	51	24	LL	Lower→Upper	IBM, PDB, PD	Yes	Alive
	P3	50/m	48	23	Distal LL	Lower→Upper	IBM	No	Alive
	P4	35/m	34	20	LL	Lower	ALS	Yes	Alive
	P5	49/m	46	30	LL	Lower→Upper	ALS, FTD	Yes	Alive
	P6	39/m	38	10	LL	Lower→Upper	ALS, FTD	Yes	Alive
HNRNPA1	P7	42/m	39	36	UL &LL	Lower + Upper	IBM	No	Alive
	P8	15/m	12	35	Distal LL	Lower→Upper	IBM	No	Alive
SQSTM1	P9	37/f	27	120	UL &LL	Lower + Upper	IBM	No	Alive
	P10[a]	45/f	36	110	LL	Lower	IBM	No	Alive
	P11	71/m	68	20	Bulbar	Bulbar→limbs	ALS	No	Mechanical ventilation
MATR3	P12	44/m	41	38	Distal LL	Lower→Upper	IBM	Yes	Alive
	P13	49/m	43	75	Distal LL	Limbs→Bulbar	IBM	No	Alive
	P14[b]	26/f	24	24	UL	Limbs→Bulbar	ALS	Yes	Death
OPTN	P15	65/f	64	20	LL	Limbs→Bulbar	ALS, FTD	No	Alive
	P16	44/m	44	5	LL	Limbs→Bulbar	ALS, FTD	No	Mechanical ventilation
	P17[c]	75/f	74	8	UL	Limbs→Bulbar	ALS	No	Death
	P18	70/m	68	30	Bulbar	Bulbar	ALS	No	Alive
	P19	68/m	64	60	UL	Upper→Lower	ALS	No	Alive
ANXA11	P20	55/m	49	70	UL	Limbs→Bulbar	IBM, ALS, FTD	No	Mechanical ventilation
	P21	66/m	66	12	Bulbar	Bulbar→limbs	ALS, FTD	No	Death
	P22	33/f	30	46	Bulbar	Bulbar→limbs	ALS	Yes	Alive
	P23	61/f	57	58	UL	Upper→Lower→Bulbar	ALS	No	Mechanical ventilation
	P24	33/m	31	46	UL	Upper→Lower→Bulbar	ALS	No	Alive
	P25	53/f	49	68	LL	Limbs→Bulbar	ALS	No	Death
	P26	52/m	50	24	Bulbar	Bulbar→Limbs	ALS	No	Death
	P27[d]	36/m	33	34	Bulbar	Bulbar→Limbs	ALS	No	Death
	P28	66/m	65	20	LL	Lower	ALS, FTD	Yes	Alive
	P29	36/m	21	180	LL	Lower→Upper	ALS	No	Alive

Notes: [a]The patient also presented with mild cognitive impairment with Montreal Cognitive Assessment (MoCA, 22/30). [b]The patient also carried mutation of *ANXA11*, c.1454G>A, p.G491R; VUS; *FUS*, NM_004960.4, c.1454delG, p.R485fs, VUS. [c]The patient also carried mutation of *MAPT*, c.2086G>A, p.G696S, VUS. [d]The patient also carried mutation of *FUS*, NM_004960.4, c.1561C>G, p.R521G, likely pathogenic.

Abbreviations: ALS, amyotrophic lateral sclerosis; IBM, inclusion body myopathy; PDB, Paget disease of the bone; FTD, frontotemporal dementia; VCP, valosin-containing protein; hnRNPA1, heterogeneous nuclear ribonucleoprotein A1; MATR3, matrin 3; MSP, multisystem proteinopathy; SQSTM1, sequestosome 1; ANXA11, annexin A11; OPTN, Optineurin; MAPT, Microtubule Associated Protein Tau; UL, upper limb onset; LL, lower limb onset; FTD, frontotemporal dementia; IBM, inclusion body myopathy.

impairment (Supplemental Figure 1). The patients' median age at onset of clinical manifestation was 44 years old (range 12–74) at the third to fifth decade mostly (Figure 1A). The median disease duration was 34 months (range, 5–180 months) (Figure 1B). Males accounted for 72.4% (21/29), and a positive family history was reported in 31.0% of patients (9/29) (Figure 1C and D). The majority of patients (72.4%) exhibited a single MSP-related phenotype, most commonly amyotrophic lateral sclerosis (ALS, 45.0%) or inclusion body myopathy (IBM, 27.5%). In contrast, 8 patients (27.6%) presented with involvement of two or more systems (Figure 1E). Notably, two patients (P2 and P20) exhibited three distinct MSP-related manifestations simultaneously (Table 1). Of them, P2 was diagnosed with IBM, PDB, and Parkinson's disease (PD), while P20 presented with IBM combined with ALS and FTD.

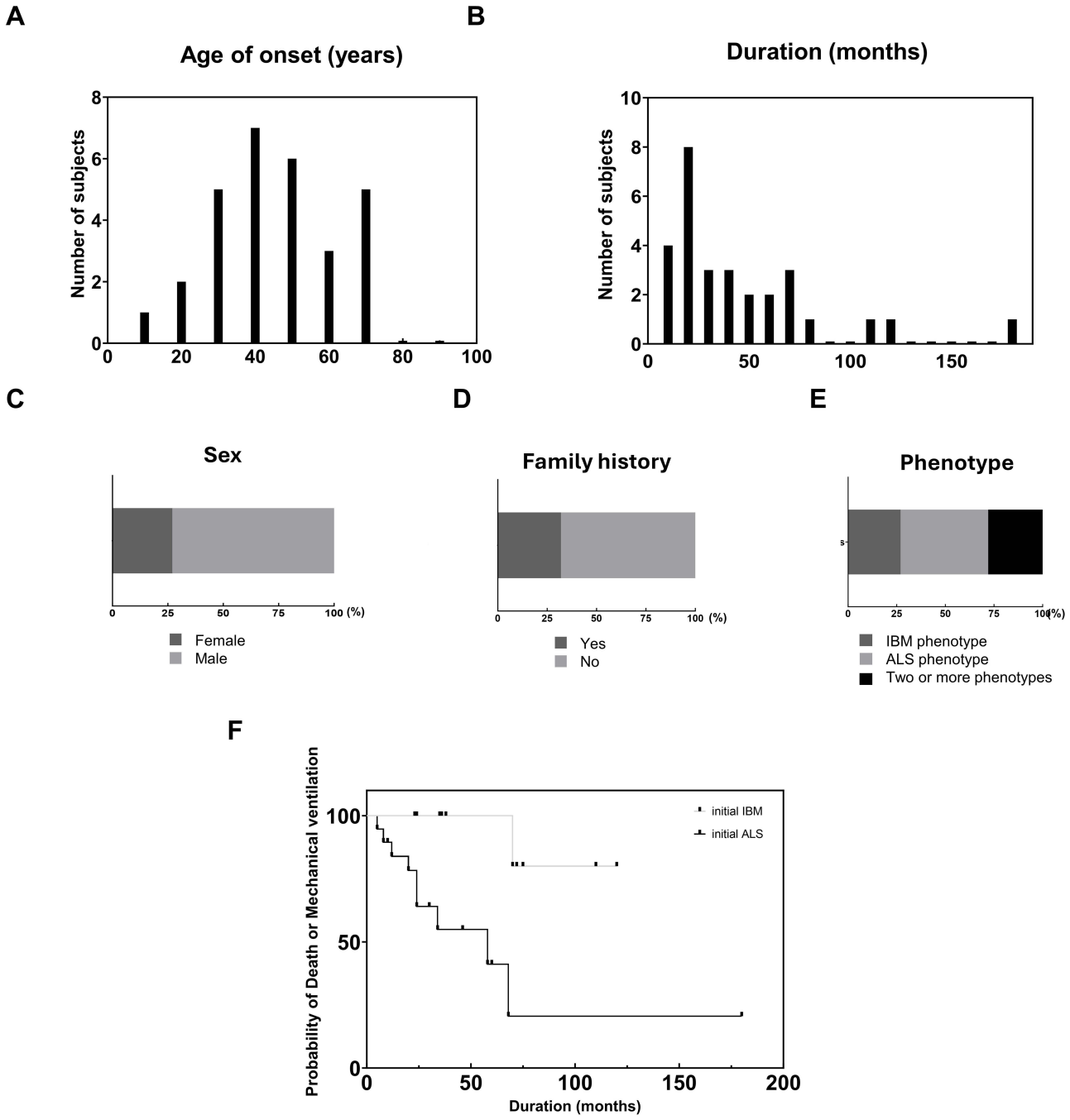

Figure 1 (**A**) Histogram of age at onset of patients. (**B**) Histogram of durations at last follow-up of patients. Sex (**C**), family history (**D**) and MSP phenotype (**E**) categories of patients. (**F**) Kaplan–Meier curves showing outcomes for presence of patients with IBM or ALS onset.

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Myopathies were observed in 10 out of 29 cases (34.5%), with a median age of onset of 43 years (range: 12–52 years). Majority of patients with myopathy (7/10) presented with initial symptoms in the lower limbs. Two patients (P7 and P9) reported simultaneous onset of weakness in both the upper and lower limbs. Half of patients primarily exhibited distal limbs muscle weakness. One patient (P15) this patient presented with upper limbs weakness and was ultimately diagnosed with IBM accompanied by ALS and FTD five years later, representing a typical case of multisystem manifestations. ALS symptoms were identified in 20 out of 29 (69.0%) patients, with a median age of onset of 52 years (range: 20–75 years). Among them, 12/20 (60.0%) patients presented with bulbar or upper-limb symptoms onset (suggestive of cervical and thoracic spinal involvement), and 8 patients (40.0%) exhibited lower limb weakness (lumbosacral spinal involvement) (Table 1). There was no significant difference in the median age at disease onset between patients with IBM onset (n = 10) and those with ALS onset (n = 19) (Mann–Whitney *U*-test, p = 0.1679). However, disease progression differed significantly between the two groups, with patients presenting with initial ALS showing a faster rate of progression to death or mechanical ventilation (Gehan-Breslow-Wilcoxon test, p = 0.0154) (Figure 1F).

Probable FTD was identified in 7/29 patients, and it consistently co-occurred with ALS (Table 1). In this subgroup of patients, the mean age was 56.6 years (range: 44–66), including 1 female and 6 males. One patient with *SQSTM1*-related IBM (P10) had a MoCA score of 22/30, suggesting mild cognitive impairment; however, the symptoms were not sufficient to support a diagnosis of FTD. The representative images of frontal-temporal lobes atrophy were showed in Figure 2. PDB was observed in only one patient (P2), a 53-year-old male who also exhibited features of IBM with variant in *VCP* gene. Elevated alkaline phosphatase (ALP, 527 U/L; upper normal limit: 125 U/L) and increased bone turnover markers were observed. Bone scintigraphy revealed cortical thickening, osseous expansion, and osteolytic changes in the pelvis, with increased tracer uptake, consistent with a diagnosis of PDB. Additionally, the patient exhibited parkinsonian features, including mild resting tremor in both hands. He responded well to dopaminergic therapy, with substantial improvement in motor symptoms.

Genetics Findings

Genetic testing identified potential pathogenic variants in all patients. Among all genotypes identified in this cohort, *VCP, ANXA11*, and *OPTN*-related MSPs were the three most prevalent subtypes, whereas no variants in *HNRNPA2B1, TIA* or *HSPB8* were detected. Specifically, variants in *ANXA11* were detected in 10 patients (34.5%), *VCP* in 6 patients (20.7%), *OPTN* in 5 patients (17.1%), *SQSTM1* in 3 patients (10.3%), *MATR3* in 3 patients (10.3%), and *HNRNPA1* in 2 patients (6.9%) (Figure 3A). Notably, one patient (P14) harbored concurrent variants in both *MATR3* and *ANXA11* (Supplemental Table 1). Among patients

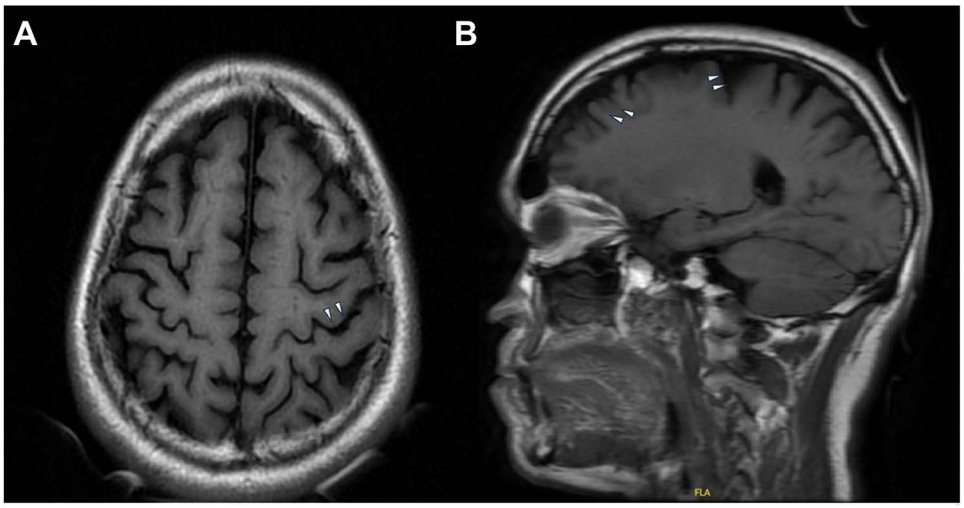

Figure 2 Brain atrophy in the MSP patient with p.D40G variant on *ANXA11*. (**A** and **B**) Magnetic resonance (MR) scan of an ALS patients with FTD from axial (**A**) and sagittal image (**B**). White arrowheads illustrated atrophy of his asymmetric frontal lobes.
Abbreviations: ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia.

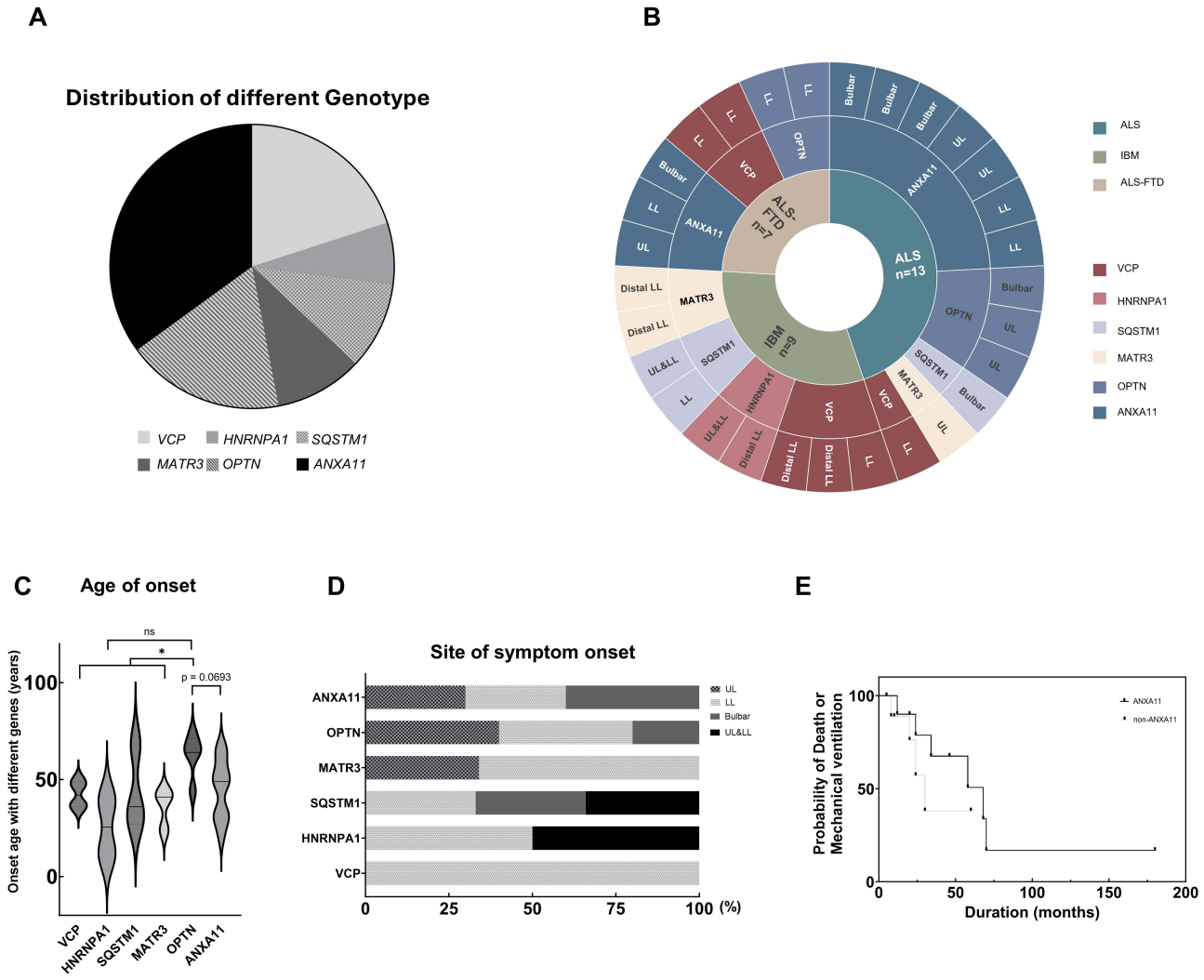

Figure 3 (**A**) The pie chart shows the relative proportions of the different genotypes. (**B**) Genotype-phenotype relation of MSP patients. Twenty-nine cases were classified into three layers according to their clinical features: main-phenotypes of MSP diseases were shown in the inner circle; the proportions of different variant types were shown in the intermediate circle; and distribution of initial involvement body regions was shown in the outermost circle. (**C**) Age of onset within different genotypes. (**D**) Sites of symptom onset in patients with different phenotypes. (**E**) Kaplan–Meier curves showing outcomes for presence of ALS patients with *ANXA11* or without *ANXA11* variants. *p value <0.05.

Abbreviations: ALS, amyotrophic lateral sclerosis; IBM, inclusion body myopathy; FTD, frontotemporal dementia; VCP, valosin-containing protein; HNRNPA1, heterogeneous nuclear ribonucleoprotein A1; MATR3, matrin 3; MSP, multisystem proteinopathy; OPTN, optineurin; SQSTM1, sequestosome 1; ANXA11, annexin A11; UL, upper limb onset; LL, lower limb onset.

presenting with an ALS phenotype, two cases (P17 and P27) were also found to carry additional potential pathogenic variants associated with ALS, including variants in *FUS* (FUS RNA Binding Protein) and *MAPT* (Microtubule Associated Protein Tau) gene (Table 1). The genotypes corresponding to different phenotypes and the initial affected sites are summarized in Figure 3B.

Phenotypes of Patients with Different Genotypes

The clinical features of patients were compared across different genotypes, including age at onset, disease duration, sex distribution, etc. (Table 2). Although some categorical or quantitative variables did not reach statistical significance across all six genotype groups, significant differences emerged in pairwise comparisons. Specifically, patients carrying *OPTN* variants exhibited a relatively later age at onset, which was higher than that observed in patients carrying *VCP* (p = 0.0260) and *MATR3* variants (p = 0.0179) (Figure 3C). The proportion of patients who died or required mechanical ventilation was 0% in the *VCP* group compared with 60% in the ANXA11 group, which was statistically significant

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Table 2 Clinical Features of Patients with Different Genotypes (N=29)

	VCP *N=6*	*HNRNPA1* *N=2*	*SQSTM1* *N=3*	*MATR3* *N=3*	*OPTN* *N=5*	*ANXA11* *N=10*	*P value*[a]
Onset-Age, median [range]	42 (34~51)	25 (12~39	36 (27~68)	41 (24~43)	64 (44~74)	49 (21~66)	0.1327
Sex (Male, n, %)	6 (100%)	2 (100%)	1 (33%)	2 (66%)	3 (60%)	7 (70%)	0.3098
Disease Duration (months), median [range]	23 (10~72)	35 (35~36)	110 (20~120)	38 (24~75)	20 (5~60)	46 (12~180)	0.2974
Cognitive impairment (n, %)	2 (33%)	0	1 (33%)	0	2 (40%)	3 (30%)	0.9512
Lower-limb onset (n, %)	6 (100%)	1 (50%)	2 (66%)	2 (66%)	2 (40%)	3 (30%)	0.0238
Mechanical ventilation or death (n, %)	0	0	1 (33%)	1 (33%)	2 (40%)	6 (60%)	0.1803

Notes: [a]Quantitative variables (onset-age, disease duration) were compared across groups using the Kruskal–Wallis test; Categorical variables (sex, lower-limb onset, and mechanical ventilation or death) were compared between groups using Fisher's exact test.

Abbreviations: ALS, amyotrophic lateral sclerosis; IBM, inclusion body myopathy; PDB, Paget disease of the bone; FTD, frontotemporal dementia; VCP, valosin-containing protein; HNRNPA1, heterogeneous nuclear ribonucleoprotein A1; MATR3, matrin 3; FUS (Fused in sarcoma), MSP, multisystem proteinopathy; OPTN, optineurin; SQSTM1, sequestosome 1; ANXA11, annexin A11; EMG, electromyogram; CK, creatine kinase. N/A, not available.

(Fisher's exact test, $p = 0.0338$). A male predominance (>60%) was observed across most genotypes, with the exception of *SQSTM1* (Table 2).

When comparing the distribution of onset sites by genotype, 100% patients with *VCP* variants presented with initial lower limb involvement, whereas those carrying *ANXA11* or *OPTN* variants predominantly showed upper limb or bulbar onset (Figure 3D). Pairwise comparisons of lower limb onset demonstrated difference between the *VCP* and *ANXA11* groups was statistically significant (Fisher's exact test, p = 0.0114). This variable also reached statistical significance across all six genotype groups (Fisher's exact test, p = 0.0238, Table 2). Additionally, upper limb and/or bulbar onset was more frequently associated with an ALS phenotype, including patients carrying *OPTN* (100%) and *ANXA11* (70%) variants. In contrast, lower limb onset was predominantly observed in patients presenting with IBM, accounting for 90% of IBM cases.

Different substitutions at amino acid position 155 of *VCP* were associated with divergent clinical phenotypes, leading to either IBM or ALS (Supplemental Table 1). Patients who initially presented with myopathy (P1) generally had a longer disease duration (72 months) and a slower disease course, whereas those presenting with ALS phenotypes experienced more rapid progression, with disease durations ranging from approximately 10 to 30 months (P5 and P6) (Table 1). Different substitutions at amino acid position 40 of *ANXA11* were identified in patients presenting with either IBM or ALS. The p.D40Y variant was observed in one patient (P20) who exhibited a complex phenotype involving IBM, ALS, and FTD. Given that 60% of patients carrying *ANXA11* variants experienced death or required mechanical ventilation, we further compared disease progression among ALS-phenotype patients with *ANXA11* variants and those with non-*ANXA11* variants. However, no significant difference in survival was observed between the two groups (Figure 3E; Gehan-Breslow-Wilcoxon test, p = 0.2453). In terms of *SQSTM1* gene, variants associated with IBM (p.A2V and p.I15L) were located closer to the N-terminus, while the ALS-associated variant (p.M404L) was located toward the C-terminus. A similar distribution pattern was observed in *MATR3*, where the IBM-associated variant was p.S85C, and the ALS-associated variant was p.K381E (Supplemental Figure 2).

Electromyographic (EMG) and Pathological Findings

Abnormalities were frequently detected in creatine kinase (CK) test, needle EMG, and muscle biopsy. Needle electromyography was performed in all 29 patients and revealed abnormal findings in every case. Neurogenic changes were observed in 19 patients (65.5%), myogenic changes in 6 patients (20.7%), and mixed patterns with both denervation and myopathic features in 4 patients (13.8%) (Table 3). *VCP, SQSTM1, MATR3* and *ANXA11*-related MSP can manifest with both neurogenic and myogenic damage. Compound muscle action potential (CMAP) analysis showed that reduced amplitude and conduction velocity were mostly observed in *ANXA11* and *OPTN*, consistent with the phenotype of motor neuron function impairments. The patients with ALS were more likely presented with abnormal CAMP, widely

Table 3 Characteristics of Auxiliary Examination Between Patients with Different Genotypes (N=29)

Index		*VCP* N=6	*HNRNPA1* N=2	*SQSTM1* N=3	*MATR3* N=3	*OPTN* N=5	*ANXA11* N=10
MUAP	Myopathic	1/6	2/2	2/3	1/3	0	0
	Neurogenic:	3/6	0	1/3	1/3	5/5	9/10
	Mixed:	2/6	0	0	1/3	0	1/10
CMAP	Reduced Amplitude:	3/6	1/2	1/3	1/3	5/5	9/10
	Reduced Conduction Velocity:	2/6	0	0	0	5/5	9/10
	Prolonged Latency:	2/6	0	0	0	5/5	9/10
Fibrillation Potentials and Sharp waves		5/6	1/2	1/3	2/3	4/5	6/10
Pattern of Muscle MRI		Distal limbs predominant	Proximal and distal limbs	Proximal and distal limbs	Bilateral adductor muscles of thigh	N/A	Bilateral posterior muscles of thigh
CK (U/L) (median, range)		368 (120~1010)	561 (538~585)	210 (137~623)	525 (157~893)	N/A	(168~627)
Muscle pathology (N=10)		N=3 RVs (100%) p62 accumulation (66%); Small angulated fibers Grouped fiber type II (33%)	N=2 RVs (100%) p62 accumulation (50%) Small angulated fibers (50%) Grouped fiber type II (0%)	N=2 RVs (100%) p62 accumulation (50%) Small angulated fibers (0%) Grouped fiber type II (0%)	N=2 RVs (100%) p62 accumulation (50%) Small angulated fibers (50%) Grouped fiber type II (50%)	N/A	N=1 RVs (0%) p62 accumulation (100%) Small angulated fibers (100%) Grouped fiber type II (100%)

Abbreviations: hnRNPA1, heterogeneous nuclear ribonucleoprotein A1; IBM, inclusion body myopathy; MATR3, matrin 3; MSP, multisystem proteinopathy; PDB, Paget disease of the bone; SQSTM1, sequestosome 1; VCP, valosin-containing protein; ANXA11, annexin A11; OPTN, Optineurin; EMG, electromyogram; CK, creatine kinase; FTD, frontotemporal dementia; IFSV, increased fiber size variation; MRC, Medical Research Council scale; NA, not available; RVs, rimmed vacuoles; MCV, motor verse conduction velocity; EMG, electromyography; CMAP, compound muscle action potential; MUAP, Motor Unit Action Potential; FTL, left frontal-temporal lobes; N/A, not available.

fibrillations and positive sharp waves in EMG, regardless of the variant subtypes. Creatine kinase (CK) was mild elevated across different genotypes, ranged from normal to 4-fold of upper limit.

Muscle biopsy was performed in 10 of 29 patients (34.5%), primarily in those presenting with myopathy at disease onset, and pathological abnormalities were identified in all cases. The most common finding was the presence of rimmed vacuoles (RVs), observed in 9 of 10 patients. Notably, muscle specimens from one patient carrying an *ANXA11* variant (P20) showed no obvious RVs on hematoxylin-eosin (H&E) or modified Gomori trichrome (MGT) staining; instead, prominent protein aggregation was observed, distinguishing this case from the others (Figure 4E). Additional pathological features included small angulated fibers in 50.0% patients (5/10), punctate p62-positive aggregates in 50.0% patients (5/10), and grouped type II fiber atrophy in 30.0% patients (3/10). Collectively, these findings suggest a combination of myogenic and neurogenic pathological changes. Representative histopathological features from selected cases are summarized in Table 3 and illustrated in Figure 4.

Discussion

Multisystem proteinopathy (MSP) has been proposed as a diagnostic framework for patients presenting with two or more core clinical manifestations, including myopathy, Paget's disease of bone (PDB), and ALS, although ALS and FTD are increasingly regarded as part of a shared disease continuum.[23] In recent years, the identification of additional disease-associated genes, such as *MATR3, OPTN*, and *ANXA11*, has further expanded the genetic landscape of MSP-like disorders. With the widespread implementation of next-generation sequencing (NGS), genetic testing is now routinely

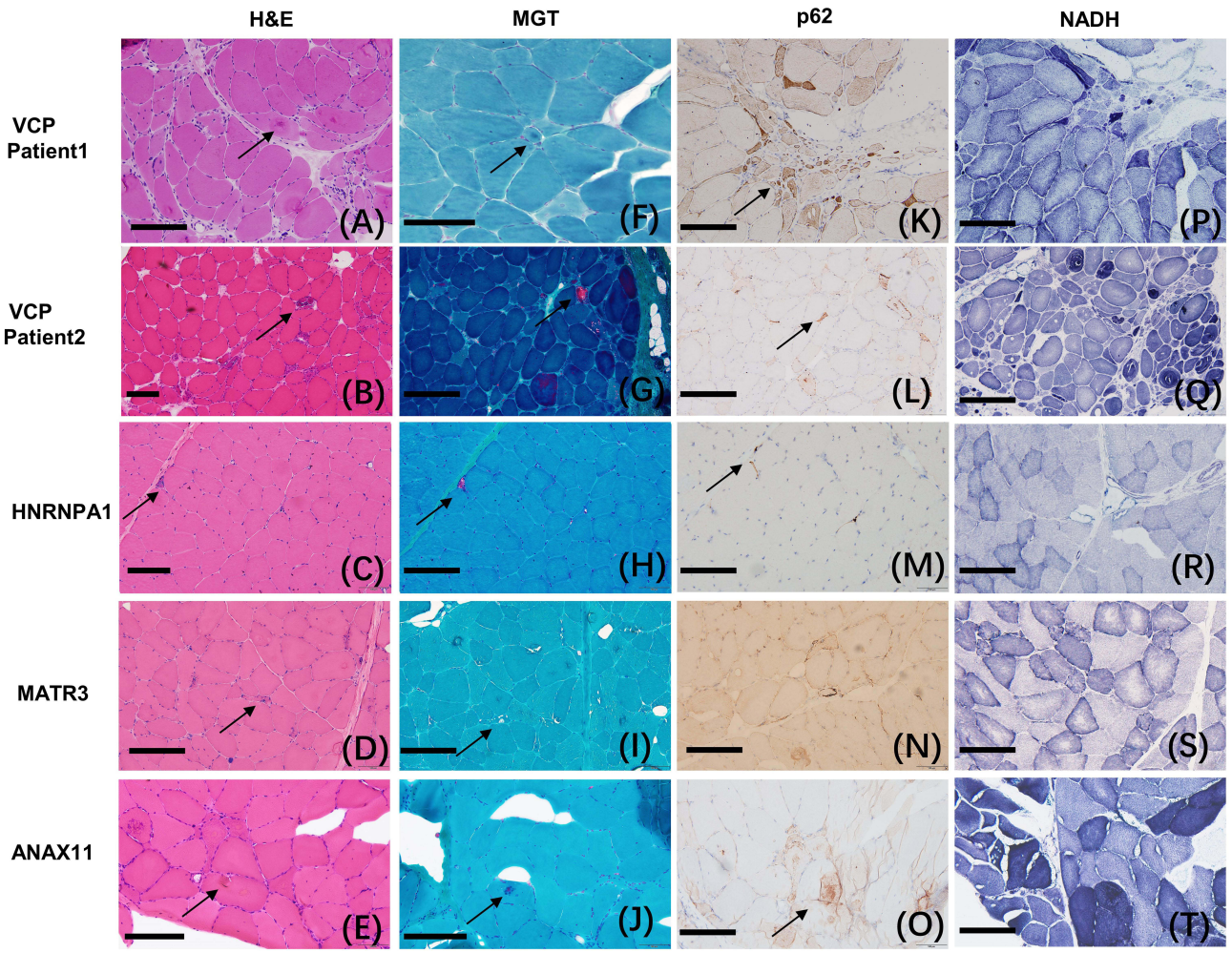

Figure 4 Myopathologic findings in patients of MSP among different genotypes. (**A**–**E**) Column A-E shows morphological changes on H&E stain from muscle biopsies from patients with variant in *VCP* (**A** and **B**), *HNRNPA1* (**C**), *MATR3* (**D**), and *ANXA11* (**E**). Abnormalities include rimmed vacuolar changes or protein aggregates (black arrow), increased fiber size variability, multiple internal nuclei, small grouped atrophy, and increased endomysial connective tissue. (**F**–**J**) MGT stain highlights the rimmed vacuoles or protein aggregates (black arrow) from patients with variant in the *VCP* gene (**F** and **G**), *HNRNPA1* (H), *MATR3* (**I**), and *ANXA11* (**J**). (**K**–**O**) Column K-O shows staining for p62 aggregates (black arrow) from patients with *VCP* (**K** and **L**) *HNRNPA1* (**M**) *MATR3* (**N**), and *ANXA11* (**O**). (**P**–**T**) Staining for NADH shows disturbed myofibrillar structure (**P**–**T**). (Scales bar = 200 μm).

Abbreviations: H&E, hematoxylin–eosin; MGT, Modified Gömöri-trichrom; NADH, reduced nicotinamide adenine dinucleotide dehydrogenase-tetrazolium reductase; *VCP*, valosin-containing protein; *HNRNPA1*, heterogeneous nuclear ribonucleoprotein A1; *MATR3*, matrin 3; *ANXA11*, annexin A11.

performed in patients presenting with suspected inherited myopathies, familial ALS, or cognitive impairment. In this study, we identified 29 patients carrying MSP or MSP-like disorder–associated variants who exhibited representative clinical phenotypes. We systematically summarized their clinical and genetic characteristics and further compared phenotypic differences across genotypes, providing an updated overview of the MSP spectrum in a Chinese cohort.

Overall, a higher proportion of patients in our cohort presented with ALS, primarily associated with *ANXA11* variants. In contrast, a study from Japan involving individuals of East Asian ancestry reported IBM as the most common initial manifestation, accounting for 74.1% of cases.[19] In that study, *VCP* variants were the most frequently identified among known pathogenic variants. As previously mentioned, not all patients carrying MSP-related variants exhibited more than one clinical manifestation. In fact, only 8 out of 29 cases (less than one-third) displayed multisystem involvement. Of these, only one patient presented with both myopathy and motor neuron symptoms, and another exhibited the multisystem involvements of IBM, PDB, and Parkinson's disease. The low proportion of patients with the classic MSP spectrum (IBM + ALS + PDB) is consistent with previous reports.[4,19]

Previous reports suggest that over 70% of patients with IBM as the initial manifestation exhibit slow progression and may remain with isolated myopathy for up to 10 years.[24] Similarly, in our cohort, secondary progression to ALS was rare among patients initially presenting with myopathy—only 1 case (P20), who carried an *ANXA11* variants, later developed ALS and FTD. *VCP* variants predominantly manifested as lower limb muscle weakness, irrespective of whether the initial phenotype was IBM or ALS. This pattern warrants further validation in larger and independent cohorts. Notably, none of the patients with VCP-related variants exhibited ophthalmoplegia or ptosis, clinical features that have been reported in previous studies.[25]

ALS was observed in association with all MSP-related variants except *HNRNPA1*. All ALS cases associated with VCP in our cohort involved substitutions at amino acid position 155. Previous studies have reported that 8 of 10 patients harboring *VCP* variants at position 155 exhibited neurogenic or mixed changes on electromyography, suggesting that this residue may confer increased susceptibility to motor neuron involvement.[26] Some patients develop ALS and others develop a myopathy is unclear, but it may be related to the presence of other inherited genetic modifiers. Given that many patients exhibited both upper and lower motor neuron signs, it was often challenging to clinically distinguish these cases from sporadic ALS.[24]

The median onset age (56.6 years old) of patients with FTD in this study seemed later than those who had IBM and PDB, with the age of onset for 43 and 42 years, respectively.[24] Consistent with previous reports, isolated FTD was rare, and most FTD cases co-occurred with additional manifestations, particularly ALS. Additionally, one patient (P2) in our cohort presented with IBM and PDB. A previous study observed that in 10 patients with *VCP* variants and 4 with *HNRNPA2B1* variants, the onset of PDB often preceded the development of muscle weakness.[26] The frequency of Parkinson disease was very low (4%) and have only been reported in association with *VCP* variants up to now.[27] Given the phenotypic overlap, genetic testing may be valuable in PD patients presenting with features of MSP or with a relevant family history.

ANXA11 has recently been recognized as a gene associated with multisystem proteinopathy disorders.[10] It was initially reported in patients with ALS, with the first identified pathogenic variant being p.D40G.[28] The N-terminal region of the ANXA11 protein contains a low-complexity domain (LCD). According to a study by Nahm et al, mutations within the LCD, such as G38R and D40G, promote ANXA11 cytoplasmic aggregation, whereas mutations in the C-terminal annexin (ANXA) domain, such as H390P and R546H, impair calcium binding.[29] These domain-specific effects may lead to distinct clinical manifestations in patients carrying LCD versus ANXA domain mutations. In a South Korean ALS cohort, Sung et al reported that ALS patients harboring ANXA11-LCD mutations had a later age at onset, more frequent bulbar onset, and more rapid early progression compared to those with ANXA domain mutations.[30] Among 5 patients carrying ANXA11 variants located in the LCD, two patients reached the endpoint of death or mechanical ventilation in this study. In comparison, among those with variants located in annexin domain, four of six patients experienced death or required mechanical ventilation. No significant distinction in disease progression was observed between variants affecting the two structural domains in the present cohort. Larger *ANXA11*-specific cohorts will be required to further clarify potential domain-dependent phenotype variability in the future. Notably, myopathy was observed only in patients carrying the p.D40Y variant, which is consistent with previous reports.[10] It remains unclear whether the p.D40Y and p.D40G variants exhibit selective involvement across the affected tissues.

The mechanisms underlying the diverse clinical phenotypes remain incompletely understood. In classic forms of MSP (*VCP, hnRNPA2B1, hnRNPA1, SQSTM1*), evidence suggests a shared molecular pathogenesis involving impairment of the ubiquitin–proteasome system and autophagy. Dysregulation of these pathways is also a central feature in both ALS and IBM, providing a mechanistic link between muscle and motor neuron involvement.[1] Recent studies have further expanded this framework by implicating ANXA11 in related pathogenic processes. Ca^{2+}-dependent interactions and co-aggregation between ANXA11 and ALS-associated RNA-binding proteins, including FUS and hnRNPA1, have been demonstrated in motor neurons and brain tissue from patients with ALS carrying *FUS* mutations, suggesting convergence on RNA metabolism and protein aggregation pathways.[29] Fibroblasts derived from patients harboring the *ANXA11* p.D40I variant exhibit defects in stress granule dynamics and impaired clearance, while muscle histopathology reveals a myopathic pattern accompanied by ANXA11 protein aggregation.[31] Moreover, functional studies in Drosophila models have shown that ANXA11 mutants specifically interact with TDP-43, a key pathological protein in ALS and

frontotemporal dementia.[32] Together, these observations suggest that *ANXA11*-related MSP may share core pathogenic pathways with classical MSP, providing a plausible explanation for the multisystem involvement associated with *ANXA11* variants.

This study has several limitations. First, not all patients underwent comprehensive cognitive assessment and brain imaging; in some cases, only cognitive screening scales were used, which may have led to an underestimation of cognitive impairment. Second, muscle biopsies were not routinely conducted in ALS patients, although these individuals were more likely to undergo brain imaging due to bulbar symptoms. Additionally, the relatively low prevalence of PDB observed in this cohort may be due to the small sample size, diagnostic challenges, and potential selection bias. As the study was conducted in a neurology clinic, patients presenting solely with PDB phenotypes were likely underrepresented or excluded. In the future, multicenter, prospective studies with multidisciplinary collaboration and standardized data collection in larger cohorts will be essential to study the natural history and explore potential biomarkers of MSP. Acquisition of primary muscle samples from patients with myopathy phenotype, may also facilitate clarifying the pathogenic of these VUS and mechanistic research on ALS, especially when access to neuronal samples is limited.

Conclusion

Our study expands the clinical and genetic spectrum of MSP and related disorders in a Chinese cohort and highlights the phenotypic variability across different genotypes, even among carriers of the same variant. Variants in *VCP* were more frequently associated with muscle involvement, and *OPTN* and *ANXA11* variants were predominantly linked to ALS-dominant phenotypes. Disease progression was more strongly associated with the initial clinical phenotype than with genotypes. These findings underscore the importance of genetic testing, particularly next-generation sequencing, in patients presenting with unexplained myopathy, motor neuron disease, or cognitive impairment, especially when multi-system involvement is suspected. Future large-scale studies are needed to validate these genotype-phenotype associations and to explore targeted therapeutic strategies.

Abbreviations

MSP, multisystem proteinopathy; IBM, inclusion body myopathy; ALS, amyotrophic lateral sclerosis; PDB, Paget disease of the bone; FTD, frontotemporal dementia; *VCP*, valosin-containing protein; *HNRNPA1*, heterogeneous nuclear ribonucleoprotein A1; *SQSTM1*, sequestosome 1; *MATR3*, matrin 3; *OPTN*, optineurin; *ANXA11*, annexin A11.

Data Sharing Statement

The data presented in the current study are available on request from the corresponding author Yi Dong.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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