

Mutational spectrum and phenotypic variability of VCP-related neurological disease in the UK

INTRODUCTION

Hereditary inclusion body myopathy (IBM) with Paget's disease of the bone (PDB) and frontotemporal dementia (FTD) (IBMPFD) is a rare autosomal dominant disorder due to mutations in the valosin-containing protein gene (*VCP*).¹ Pathogenic *VCP* variants have also been associated with amyotrophic lateral sclerosis² and other phenotypes including dilated cardiomyopathy and Parkinson's disease. We describe phenotypic and genetic findings of 42 individuals from 21 families with *VCP* mutations. As our service is the reference laboratory for the UK, we calculated the UK's point prevalence based on the 2011 Census as the number of cases per population.

RESULTS

In total, 42 individuals were identified, 23 men and 19 women from 21 kinships (see online supplementary tables S1A, B). Based on our data, the expected point prevalence of IBMPFD in the UK is 0.066/100 000 population.

Eighteen unrelated patients harbour a previously described mutation. In addition, three patients from two families harbour two novel variants (c.604G>T, p.G202W in exon 6 and c.1316C>G, p.A439G in exon 11) that are predicted to be pathogenic by in silico analysis (Alamut interpretation software V2.4) and segregate with disease. Three previously described

mutations were identified in exon 5 of the *VCP* gene. The mutation p.R155H (c.464G>A) was found in 11 families. The mutation p.R191Q (c.572G>A) was found in three unrelated patients, p.R155C (c.463C>T) in two families, and p.R93C (c.277C>T) in two unrelated patients (see online supplementary material genetic analysis and mutation analysis).

The mean age of disease onset was 42.05 ± 7.94 years. Three individuals were tested as part of a family screening and were asymptomatic at the ages of 21, 23 and 31 years.

Muscle weakness was the first manifestation (figure 1) in 92.3% of patients, PDB was the first symptom in one case, and in two cases we were unable to obtain this information. Proximal weakness of both limb girdles was the presentation in 27% of patients; 21.6% presented with proximal upper limb weakness, and 13.5% with proximal lower limb weakness. A combination of distal and/or proximal upper and/or lower limb weakness at onset was seen in 24.2%. In two patients, falls were the first reported symptom.

Twenty-three patients remained ambulant after 15.7 ± 8.2 years (range 5–39). The mean time to loss of ambulation was 13.37 ± 6.6 years (range 5–22 years). Of the 10 non-ambulant patients, 6 (60%) experienced some degree of cognitive decline compared with 33.3% of the ambulant patients.

Additional clinical findings (see online supplementary table S2) were scapular winging in 20 patients (50%), markedly atrophic hands in 6 patients (15.4%), camp-tocormia, or bent spine, in 6 (15.4%), finger extensor weakness in 5 (12.8%), facial weakness in 3 (7.7%) and weakness

of abdominal muscles in two patients (5.1%). An asymmetric pattern of muscle involvement was present in nine patients (23%). Nine patients (23%) experienced sphincter or erectile dysfunction. Two patients were diagnosed with rheumatoid arthritis and two with Parkinson's disease. Back pain (4 patients), cramps and muscle pain (12 patients) were frequently reported.

Forced vital capacity systematically assessed in 20 patients, was reduced in 2, requiring non-invasive ventilation after, respectively, 16 and 18 years of disease duration. ECG was performed in 14 patients. Three patients from the same family had moderate left ventricular dysfunction, 10, 11 and 17 years after the first symptoms. For the last patient, there was a past history of myocardial infarct (MCI). Severe progressive FTD or MCI was observed in 14 of 29 patients (48.2%); in 5 patients, data were not available. PDB was confirmed in eight patients, and five other reported bone pain. In three cases, despite normal X-rays, bone alkaline phosphatase serum levels were high.

Serum creatine kinase (CK) levels were measured in 19 of 40 patients. In 13 patients (68.4%), CK levels were mildly raised with a mean value of 379.6 ± 142.1 U/L (N=0–150), and a range between 162 and 725 U/L. Neurophysiological data were available for 19 of 39 patients. Myopathic changes were reported in 10 of these patients, 5 presented a neurogenic pattern and 4 patients, a mixed myopathic and neurogenic pattern. Muscle biopsies, available for 17 patients, showed mild, unspecific myopathic changes except for 1, which showed a dystrophic pattern. Eleven biopsies (61%) revealed rimmed vacuoles.

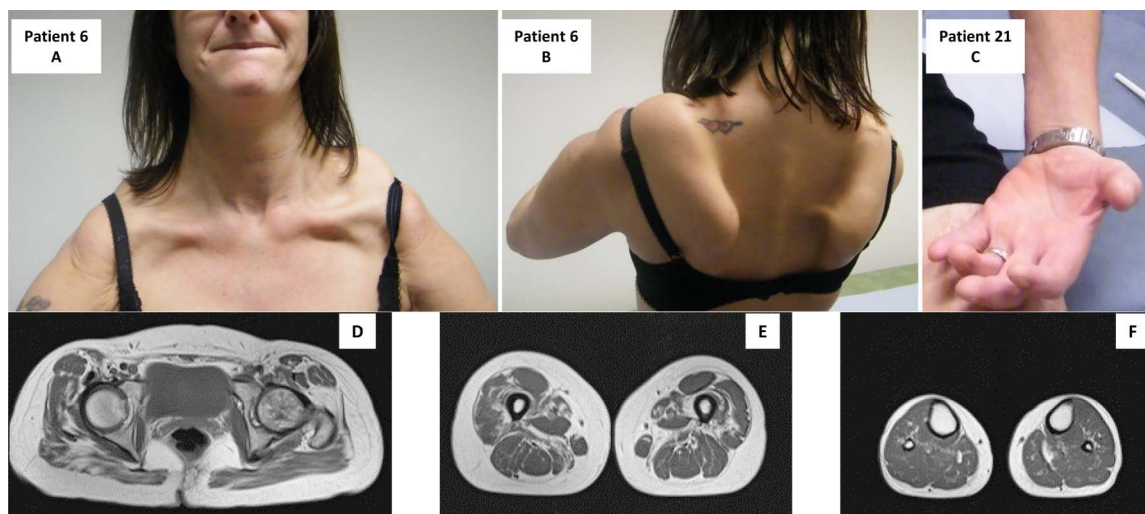


Figure 1 Patient 6 illustrates a pseudo-FSHD pattern. Note the scapular involvement (A) and pronounced scapular winging (B). Patient 21: note the wasting of the forearm and thenar eminence (C). Muscle MRI of pelvic girdle (D), thigh (E) and lower leg (F), showing mild fatty infiltration of Gluteus, more pronounced fatty infiltration of vastus lateralis, vastus medialis, adductor magnus and sartorius.

DISCUSSION

At present, only 43 families with VCP mutations have been reported worldwide to the Leiden Open Variation Database (LOVD). Our data indicate a point prevalence of IBMPFD of 0.066/100 000 for the UK population as a whole. Although we accept that these figures need to be interpreted with caution, and cases may remain unrecognised, they suggest that IBMPFD is a very rare disease. As our department is a specialised service for muscle diseases, it is not surprising that muscle weakness was the first symptom in the majority of patients; with either a limb-girdle or combined proximal-distal distribution. Distal weakness, mostly affecting the small hand muscles, generally an extremely rare presentation of myopathy, was identified in several patients with IBMPFD.

Approximately half of our patients remained ambulant after 17.8 ± 7.5 years. Dementia, or MCI, seems to correlate with the severity of the disease, as 60% of our patients with dementia or MCI were non-ambulant, compared with 33.3% of the patients without cognitive decline. This data on rate of progression is similar to previous reports.³

By comparison, the number of patients with respiratory or cardiac insufficiency was relatively low. They constitute the main cause of death in IBMPFD,³ and should be regularly monitored.

The presence of sphincter and erectile dysfunction, and of Parkinson's disease, further expands the phenotypic characteristics of IBMPFD. Parkinson's disease has recently been recognised as a clinical manifestation of VCP-related disease.^{3,4}

The presence of rimmed vacuoles, although non-specific, remains the major histological hallmark of IBMPFD.

The identification of mutations in different exons emphasises that full gene sequencing is required to exclude VCP-related disease. Owing to multisystem involvement, this disease should perhaps be called VCP-related disease to try to encompass the muscle, bone and central nervous system manifestations.

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Genetic Analysis

DNA samples were analyzed by bi-directional fluorescent sequencing of all 17 exons of the VCP gene. Primer sequences were designed using the Primer-3 Plus program and are available upon request. PCR reaction mix consisted of 50ng genomic DNA, 0.1 µmol of each primer, and Immolase (Bioline) in a reaction mix of 20µl. Amplification of exon 1 contained an additional 15% DMSO. Denaturation was performed at 95°C for 4 min and then followed by 32 cycles of 94°C for 1min, 60°C for 1min, and 72°C for 1min, with a final extension step of 72°C for 10 min.

PCR products were sequenced with the BigDye Terminator 3.1 Cycle Sequencing Kit (Applied Biosystems). Sequencing reactions were size-separated on an Applied Biosystems 3500 xL Genetic Analyzer. Sequence data was analyzed with Mutation Surveyor version 4.0.8 software (Soft Genetics). Nomenclature was based on sequence accession number NM_007126.3 where the A of the initiation codon ATG is nucleotide 1.

Mutation analysis

In addition, three unrelated patients referred for VCP testing were found to have variants of unknown clinical significance: c.1360-14C>G, c.2214A>G and c.2316-46C>T. None of these three patients had a clinical phenotype strongly suggestive of IBMPFD. The c.2214A>G synonymous substitution is not predicted by bioinformatic analysis to be pathogenic. The intronic variants c.1360-14C>G and c.2316-46C>T are predicted by bioinformatic analysis to have a potential impact on splicing and we are aiming to undertake RNA studies to investigate these variants further once samples become available.

Table 1.a – Demographic, clinical and molecular data

Family no. or sporadic case; hereditary pattern	Case no.	Gender	Age/Age at onset (y)	WCB (y after onset)	Mode of onset (muscle weakness)	Follow-up (muscle weakness)	Mutation
I; AD	1	M	21 / (*)	(*)	(*)	(*)	p.R155C
	2	F	45/35	Yes (6 y)	Proximal UL	Proximal: UL/LL; Distal: UL>LL	p.R155C
	3	F	ψ 55/40	No	Proximal UL	Proximal: UL/LL	p.R155C
	4	M	ψ 56/39	Yes(7 y)	Proximal UL	Proximal: UL/LL	p.R155C
	5	M	ψ 63/40	Yes(22 y)	Proximal LL	Proximal: UL/LL	p.R155C
II; AD	6	F	41/33	No	Proximal UL / LL	Proximal UL/LL	p.R155H
	7	M	ψ 59/53	No	Distal LL	Distal: UL/LL	p.R155H
	8	F	31/(*)	(*)	(*)	(*)	p.R155H
	9	F	59/30	No	Proximal LL	Proximal: UL/LL	p.R155H
III; AD	10	M	56/40	No	Proximal UL / LL	Proximal UL/LL	p.R155H
	11	M	52/34	No	Proximal UL / LL	Proximal UL/LL; Distal LL>UL	p.R155H
	12	F	73/55	Yes(10 y)	Proximal UL / LL	Proximal UL/LL	p.R155H
	13	M	54/28	Yes(20 y)	Proximal UL / LL	Proximal: UL/LL; Distal: LL>UL	p.R155H
	14	F	57/35	No	Proximal UL / LL	Proximal: UL/LL; Distal: LL>UL	p.R155H
	15	F	52/42	No	Proximal UL	Proximal: UL/LL	p.R155H
	16	F	56/30	No	Proximal UL	Proximal: UL/LL; Distal: UL/LL	p.R155H
	17	F	53/33	No	Proximal UL / LL	Proximal: UL/LL; Distal: UL>LL	p.R155H
	18	M	38/31	Yes(5 y)	Proximal LL	Proximal: UL/LL; Distal: UL>LL	p.R155H
Case; sporadic	19	M	54/32	Yes(19 y)	Distal UL / LL	Proximal: UL/LL; Distal: UL/LL	p.R155H
Case; sporadic	20	F	66/52	No	Proximal UL	Proximal: UL>LL; Distal: UL/LL	p.R155H
Case; sporadic	21	M	53/45	No	Distal UL	Proximal: UL/LL; Distal: UL>LL	p.R191Q
Case; sporadic	22	M	56/42	No	Distal LL	Proximal: UL/LL; Distal: LL>UL	p.R93C
Case; sporadic	23	M	62/54	No	Distal LL	Distal: LL>UL, Proximal: UL>LL	p.R155C
IV; AD	24	M	ψ/(-)	(-)	(-)	(-)	p.R155H
	25	M	23/(*)	(*)	(*)	(*)	p.R155H
Case; sporadic	26	M	57/48	No	Proximal UL / LL	Proximal: LL>UL	p.R155H
Case; sporadic	27	M	46/35	No	Proximal UL / LL	Proximal: UL/LL + distal LL	p.R155H
Case; sporadic	28	F	58/49	No	Proximal UL	Proximal + distal: UL; Proximal: LL	p.R155H
Case; sporadic	29	F	Ψ56/36	No	(-)	(-)	p.R155H
Case; sporadic	30	F	50/42	No	Falls;	Proximal UL>LL	p.R155H
Case; sporadic	31	F	55/46	No	Proximal UL / LL	Proximal UL<LL	p.R155H
Case; sporadic	32	M	63/54	No	Proximal LL	Proximal UL/LL	p.R191Q
Case; sporadic	33	F	ψ67 /48	No	Distal LL>UL	Proximal LL>UL ; distal UL/LL	p.R93C
Case; sporadic	34	M	62/48	(-)	Proximal UL / LL	Proximal UL/LL; Distal UL	p.R191Q
Case, AD - probable	35	F	Ψ78/50	Yes(-)	Proximal UL; Distal LL	Proximal +distal: UL/LL	p.G202W
V; AD – probable	36	M	79/40	No	Proximal UL	Proximal: UL> LL Distal: LL> UL	p.A439G
	37	M	ψ66/41	No	Distal UL	Proximal: UL/LL	p.A439G
VI; AD	38	M	56 / 42	No	Proximal LL	Proximal: LL/UL	p.R155H
	39	F	63 / 58	No	Falls	Proximal: LL>UL; Distal: LL	p.R155H
	40	F	57 / 38	No	Distal UL	Distal> proximal: UL and LL	p.R155H
	41	M	Ψ58/40	Yes (18)	Proximal LL	Generalized UL>LL, Proximal>distal	p.R155H
	42	M	Ψ61/(60)	Yes (-)	(-)	(-)	p.R155H

Legend: F, female; M, male; y: years; (*), asymptomatic; ψ, deceased; WCB, Wheelchair Bond; UL, upper limbs; LL, lower limbs; (-), missing data; AD, autosomal dominant

Table 1.b– Demographic, clinical and molecular data

Case no	Last FVC	Echocardiogram	Cognitive impairment	Sphincter involvement	CK U/L (N<150)	PDB /High ALP	Mutation
2	Normal	(-)	Yes	No	Normal	(-)	p.R155C
3	(-)	(-)	No	No	Normal	(-)	p.R155C
4	(-)	(-)	Yes	No	(-)	(-)	p.R155C
5	(-)	(-)	Yes	No	350	(-)	p.R155C
6	94%	(-)	No	No	(-)	Yes/Yes	p.R155H
7	(-)	(-)	(-)	No	(-)	Yes/Yes	p.R155H
9	(-)	(-)	No	No	Normal	(-)	p.R155H
10	101%	Normal	(-)	Yes	500	(-)	p.R155H
11	76%	Reduced left ventricle function	(-)	Yes	500	No/Yes	p.R155H
12	109%	Moderate left ventricle systolic dysfunction	Yes	Yes	280	No/Yes	p.R155H
13	111%	Moderate left ventricle systolic dysfunction	No	Yes	238	(-)	p.R155H
14	50%	(-)	No	Yes	(-)	(-)	p.R155H
15	119%	(-)	No	Yes	(-)	(-)	p.R155H
16	132%	(-)	No	No	(-)	Yes/Yes	p.R155H
17	Normal	(-)	No	Yes	(-)	(-)	p.R155H
18	80%	(-)	No	No	725	(-)	p.R155H
19	Normal	(-)	Yes	No	299	(-)	p.R155H
20	Normal	(-)	No	No	287	(-)	p.R155H
21	111%	(-)	No	No	(-)	(-)	p.R191Q
22	107%	(-)	Yes	No	400	No/Yes	p.R93C
23	75%	Normal	Yes	No	Normal	Yes/Yes	p.R155C
24	(-) Respiratory involvement	(-)	(-)	No	(-)	(-)	p.R155H
26	100%	(-)	No	No	(-)	Yes/Yes	p.R155H
27	100%	Abnormal	No	No	500	(-)	p.R155H
28	(-)	(-)	No	No	Normal	(-)	p.R155H
29	(-)	(-)	Yes	No	(-)	Yes/Yes	p.R155H
30	(-) Respiratory involvement	Normal	(-)	No	Normal	(-)	p.R155H
31	100%	(-)	Yes	No	Normal	No/No	p.R155H
32	85%	Normal	Yes	No	(-)	Yes/Yes	p.R191Q
33	86%	Normal	Yes	Yes	Normal	No/No	p.R93C
34	100%	Normal	Yes	No	(-)	No/No	p.R191Q
35	100%	Normal	Yes	No	Normal	(-)	p.G202W
36	100%	Normal	(-)	No	391	No/No	p.A439G
37	(-)	(-)	Yes	Yes	162	No/No	p.A439G
38	(-)	Normal	No	No	(-)	(-)	p.R155H
39	97%	(-)	(-)	(-)	303	(-)	p.R155H
40	78%	Normal	No	No	Normal	(-)	p.R155H
41	Ventilated	Normal	No	No	500	(-)	p.R155H
42	(-)	(-)	(-)	(-)	(-)	(-)	p.R155H

Legend: F, female; M, male; y, years; PDB, Paget disease of the bone; ALP, Alkaline Phosphatase; FVC, Forced Vital Capacity (% of predicted); (-), missing data;

Table 2 – Additional clinical findings

Additional clinical findings	(n)	%
Scapular winging	20	50%
Muscle pain and/or cramps	12	30.7%
Asymmetrical involvement	9	23%
Sphincter dysfunction	9	23%
Camptocormia or bent spine	6	15.4%
Atrophic hands	6	15.4%
Finger extensors weakness	5	12.8%
Autonomic, sensory and motor neuropathy	3	7.8%
Facial weakness	3	7.7%
Abdominal wall weakness	2	5.1%
Deafness	2	5.1%
Rheumatoid arthritis	2	5.1%
Ptosis + external ophtalmoparesis	1	2.6%
Bull's eye maculopathy	1	2.6%
Gynecomastia	1	2.6%
Sleep apnoea	1	2.6%
Rigid spine	1	2.6%
Hand tremor	1	2.6%
Parkinson's Disease	1	2.6%

Legend: Additional clinical findings reported in our cohort.
(n) Number of affected. % = (n)/39