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ORIGINAL COMMUNICATION

A novel exon 2 I27V VCP variant is associated with dissimilar clinical syndromes

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Abstract Mutations in valosin-containing protein (VCP) are associated with a syndromic constellation of inclusion body myositis, Paget's disease of bone and frontotemporal dementia. Here we describe the case reports of two patients with a novel variation (p.I27V) in the VCP gene that was not identified in a healthy control population. One patient presented with a frontotemporal dementia syndrome associated with raised serum alkaline phosphatase and a family history of progressive muscle disease and behavioural decline, while the second patient presented with isolated progressive dysarthria. Together these cases suggest a potential for the same VCP mutation to produce distinct patterns of brain damage, underlining the clinical heterogeneity of VCP-associated disease.

Keywords Frontotemporal dementia · Valosin-containing protein · Frontotemporal lobar degeneration · IBMPFD · Motor neurone disease

Introduction

Mutations in valosin-containing protein (VCP) have been shown to be associated with a constellation of disorders which frequently co-occur: inclusion body myositis, Paget's disease of the bone and frontotemporal dementia (IBMPFD) [1–3]. More recently, it has been suggested that they are also a cause of familial motor neurone disease (MND)/amyotrophic lateral sclerosis (ALS) [4]. Currently, 17 mutations in VCP are described (http://www.molgen.ua.ac.be/FTDMutations). Mutations were originally described in exons 3, 5, 6 and 10 of the VCP gene, and more recently, also in exons 4, 7 and 11. Both IBMPFD and MND/ALS overlap pathologically with frontotemporal lobar degeneration (FTLD) being associated with ubiquitin-positive, TDP-43-positive neuronal inclusions on pathological examination [5–7]. VCP mutations are rare in large series of patients with FTLD (or MND/ALS) and the phenotypic spectrum continues to be delineated [4, 8, 9]. Here we describe two patients in association with a novel VCP variant in exon 2.

Case descriptions

Case 1

This man developed progressive cognitive difficulties from the age of 55 years. He took early retirement from his job as a telephone operator as he was unable to learn the new skills required with computerised procedures and subsequently complained of an insidious deterioration in episodic memory. At the same time he developed progressive behavioural disturbance, gradually withdrawing from social activity and developing paranoid ideas (he became convinced, erroneously, that thieves were trying to break into his car). From the age of 63, he became slower physically with decreased mobility, difficulty using his hands and the development of a mild tremor which did not

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respond to levodopa therapy. His father had died at the age of 67 with a neurodegenerative disorder characterised by progressive muscle weakness accompanied by personality change and aggression, and had received a diagnosis of "progressive muscular atrophy".

When initially assessed at the age of 65, he had a symmetrical akinetic rigid syndrome with myoclonus in the upper limbs and bilateral limb apraxia. Neuropsychological assessment revealed a verbal IQ of 84 and performance IQ of 73. Verbal subtest scores were defective for arithmetic, low average for similarities and digit span and average for vocabulary whilst performance subtest scores were all low average apart from block design which was defective. He scored at an impaired level on tests of both verbal and visual episodic memory (Warrington Short Recognition Memory Test for Words and Faces) and had decreased verbal fluency. However, he had intact naming (at the 90th percentile on the Graded Naming Test) and reading (high average performance on the National Adult Reading Test). Blood screens were normal apart from a raised serum ALP (193 IU/L; normal range 40–100 IU/L). Brain MRI showed marked symmetrical cerebral atrophy involving the frontal and parietal lobes. Brain SPECT revealed bilateral parietal lobe hypometabolism. He was subsequently lost to follow-up.

Case 2

This woman developed progressive speech disturbance beginning at the age of 72 years with a tendency to stumble over polysyllabic words. Her first language was English but she spoke fluent French and noticed that her French accent had deteriorated. Over the following 3 years her speech became increasingly hesitant and effortful but without speech errors or word-finding difficulty, nor other cognitive complaints. There was no known family history of neurological illness although her father had committed suicide in his mid 50s and she had lost touch with her father's family. Her mother's sister and four maternal cousins had a developmental stutter.

When initially assessed at the age of 75 her speech was dysarthric, effortful and dysprosodic but there was no language impairment. The neurological examination was otherwise normal (in particular, there were no extrapyramidal or cerebellar signs). On neuropsychological assessment, episodic memory, naming, reading, visuospatial skills and executive function were normal. Blood screens including serum ALP and brain MRI at this time were normal. Over the following 3 years she exhibited a slowly progressive dysarthria without the development of any linguistic impairment or other cognitive or neurological features. Repeat blood screens 3 years after the initial assessment revealed raised serum ALP (139 IU/L) and inflammatory markers (CRP 90, ESR 47); serum CPK was normal (119). Electromyography was normal; in particular, there was no evidence of myopathy.

Genetic analysis

Both patients were screened for mutations in progranulin, MAPT, and VCP genes as part of a previously published study of 225 patients with a degenerative disorder within the FTLD spectrum [8]. This study was approved by the National Hospital for Neurology and Neurosurgery Local Research Ethics Committee. Both patients were found to have the same variant in exon 2 of the VCP gene (p.I27V, c.79A>G, CCDS ID 6573). This mutation was not found in 451 healthy UK blood donor samples obtained from the European Collection of Cell Cultures (ECACC) matched for ethnicity.

Discussion

VCP mutations have been described in exon 3 (R93C, R95G, R95C), exon 4 (P137L), exon 5 (R155C, R155H, R155S, R155P, G157R, R159C, R159H, R191Q), exon 6 (L198W, A232E), exon 7 (T262A), exon 10 (N387H) and exon 11 (A439S) (http://www.molgen.ua.ac.be/FTDMutations). In the absence of samples from other family members to show segregation, we cannot be certain of the pathogenicity of I27V. The absence of the I27V variant in the healthy control population screened here does not exclude the possibility that this is a rare neutral polymorphism in the British population. Suggestive evidence can be provided by algorithms which predict pathogenicity based on the similarity of amino acids changed in the context of the predicted protein structure and evolutionary conservation. However, these algorithms, such as PolyPhen, are inaccurate [10]. From mutation series listed above, only R155C and R159C are regarded as probably pathogenic by PolyPhen, and G157R possibly pathogenic, therefore *in silico* prediction of pathogenicity at this gene is not likely to be reliable. Hence, although the family histories in our cases coupled with ancillary laboratory findings (in particular, raised serum ALP) are consistent with a pathogenic role for the I27V variant, further corroboration will be necessary to confirm this.

If VCP mutations cause IBMPFD mean age of clinical onset is in the fifth decade most commonly with a myopathy. However, the age of onset ranges widely from the third to the eighth decades and the disease may present with Paget's disease of bone or frontotemporal dementia as the first syndrome [1–3]. Disease duration is also variable with some patients living over 30 years from onset. The characteristic triad of myopathy, Paget's disease and dementia occurs in a minority of cases: whereas over 90%

of patients have a myopathy, Paget's disease has been reported in around half the cases and dementia in only around a third of cases (though cognitive decline may occur late in the course) [3]. Laboratory features are similarly of variable diagnostic utility: while serum ALP is usually raised in association with Paget's disease of the bone, serum CPK may be normal even in cases with myopathy. The clinical spectrum has recently been extended by the association of VCP mutations with MND/ALS [4]. Although data are relatively limited currently, it appears that patients with VCP-related MND/ALS may present with either limb or bulbar onset of symptoms indistinct from the features of sporadic MND/ALS [4].

Conclusions

The present cases together underline the potential phenotypic variability of VCP mutations. Case 1 presented with a frontotemporal dementia syndrome with raised serum ALP and a family history of progressive muscle disease and behavioural decline, while Case 2 exhibited an isolated progressive dysarthria also associated with raised serum ALP. If indeed the pathogenetic role of the p.I27V variant is substantiated in future work, these cases suggest that the same VCP mutation can produce strikingly divergent patterns of brain damage. This phenotypic variation may in turn depend on additional unidentified genetic or environmental factors, in keeping with the heterogeneity of tissue types affected by VCP-associated disease.

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Conflict of interest None.

References

1. Watts GD, Wymer J, Kovach MJ, Mehta SG, Mumm S, Darvish D, Pestronk A, Whyte MP, Kimonis VE (2004) Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. Nat Genet 36(4):377–381
2. Guinto JB, Ritson GP, Taylor JP, Forman MS (2007) Valosin-containing protein and the pathogenesis of frontotemporal dementia associated with inclusion body myopathy. Acta Neuropathol 114(1):55–61
3. Weihl CC, Pestronk A, Kimonis VE (2009) Valosin-containing protein disease: inclusion body myopathy with Paget's disease of the bone and fronto-temporal dementia. Neuromuscul Disord 19(5):308–315
4. Johnson JO, Mandrioli J, Benatar M, Abramzon Y, Van Deerlin VM, Trojanowski JQ, Gibbs JR, Brunetti M, Gronka S, Wuu J, Ding J, McCluskey L, Martinez-Lage M, Falcone D, Hernandez DG, Arepalli S, Chong S, Schymick JC, Rothstein J, Landi F, Wang YD, Calvo A, Mora G, Sabatelli M, Monsurrò MR, Battistini S, Salvi F, Spataro R, Sola P, Borghero G, ITALSGEN Consortium, Galassi G, Scholz SW, Taylor JP, Restagno G, Chiò A, Traynor BJ (2010) Exome sequencing reveals VCP mutations as a cause of familial ALS. Neuron 68(5):857–864
5. Forman MS, Mackenzie IR, Cairns NJ, Swanson E, Boyer PJ, Drachman DA, Jhaveri BS, Karlawish JH, Pestronk A, Smith TW, Tu PH, Watts GD, Markesbery WR, Smith CD, Kimonis VE (2006) Novel ubiquitin neuropathology in frontotemporal dementia with valosin-containing protein gene mutations. J Neuropathol Exp Neurol 65(6):571–581
6. Neumann M, Mackenzie IR, Cairns NJ, Boyer PJ, Markesbery WR, Smith CD, Taylor JP, Kretzschmar HA, Kimonis VE, Forman MS (2007) TDP-43 in the ubiquitin pathology of frontotemporal dementia with VCP gene mutations. J Neuropathol Exp Neurol 66(2):152–157
7. Cairns NJ, Bigio EH, Mackenzie IR, Neumann M, Lee VM, Hatanpaa KJ, White CL 3rd, Schneider JA, Grinberg LT, Halliday G, Duyckaerts C, Lowe JS, Holm IE, Tolnay M, Okamoto K, Yokoo H, Murayama S, Woulfe J, Munoz DG, Dickson DW, Ince PG, Trojanowski JQ, Mann DM, Consortium for Frontotemporal Lobar Degeneration (2007) Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration. Acta Neuropathol 114(1):5–22
8. Rohrer JD, Guerreiro R, Vandrovcova J, Uphill J, Reiman D, Beck J, Isaacs AM, Authier A, Ferrari R, Fox NC, Mackenzie IRA, Warren JD, de Silva R, Holton J, Revesz T, Hardy J, Mead S, Rossor MN (2009) The genetics and heritability of frontotemporal lobar degeneration. Neurology 73(18):1451–1456
9. Seelaar H, Schelhaas HJ, Azmani A, Küsters B, Rosso S, Majoor-Krakauer D, de Rijik MC, Rizzu P, ten Brummelhuis M, van Doorn PA, Kamphorst W, Willemsen R, van Swieten JC (2007) TDP-43 pathology in familial frontotemporal dementia and motor neuron disease without progranulin mutations. Brain 130(Pt 5):1375–1385
10. Sunyaev SR, Eisenhaber F, Rodchenkov IV, Eisenhaber B, Tumanyan VG, Kuznetsov EN (1999) PSIC: profile extraction from sequence alignments with position-specific counts of independent observations. Protein Eng 12:387–394