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Letter to the Editor

Valosin-containing protein mutation and Parkinson's disease

The etiology of Parkinson's disease (PD) is unknown but it is increasingly clear that genetic factors play an important role. In addition to monogenic forms of parkinsonism, there are also other inherited conditions that may present with parkinsonism or mimic classical PD. Valosin Containing Protein (VCP) is a member of the type II AAA ATPases and is associated with a rare autosomal dominant disease characterized by inclusion body myopathy, Paget's disease of bone and Frontotemporal dementia (IBMPFD) [1]. We present a case of PD associated with a VCP gene mutation.

1. Case report

The patient is a 54 year old American man with confirmed R159C VCP gene mutation [2] and a significant history of IBMPFD in 12 family members throughout five generations (Fig. 1a and Table 1). The family is of a mixed European background, and the first affected individual was likely of German descent.

He first presented at age 44 years with decreased driving ability in his left arm while golfing. This progressed over the next year to involve rigidity, decreased dexterity and rest tremor of the left arm. He was diagnosed with PD and has since then followed a typical disease course with sustained responsiveness to dopaminergic medications and mild motor fluctuations, including mild dyskinesias and wearing off. He also developed impulse control disorder and gambling while being treated with dopamine agonists that resolved on lower doses. Other symptoms of PD began to develop, including mild dysarthria and hypophonia, micrographia, anxiety, fatigue and sleep disturbance with likely REM behavioral sleep disorder. There were no atypical features such as early falls, autonomic dysfunction, visual disturbance, psychiatric or cognitive dysfunction. Medication regimen 10 years after symptom onset include carbidopa/levodopa/entacapone 100 mg, carbidopa/levodopa CR 50/200 0.5 tabs, ropinerole 1 mg, amantadine 100 mg all taken every 4 h for a total of four doses daily. Additional medications include alprazolam 0.25 mg daily as needed and quetiapine 50 mg at night for RBD. An on/off levodopa evaluation, 10 years after symptom onset, revealed continued responsiveness to levodopa. Total UPDRS score in the OFF state was 31 with a motor sub-score of 14, 10 h after last medication dose. Examination in the ON state 1 h after taking medications revealed a motor UPDRS sub-score score of 4 and a total score of 20. There were also mild diffuse dyskinesias. Other family members have also been examined, but did not reveal any signs of parkinsonism.

There were subjective complaints of mild forgetfulness but an evaluation by a neurobehavior specialist revealed essentially normal cognition with only mildly decreased abstract verbal fluency and visuospatial processing. MMSE was 30/30. However, despite his current normal mental status, it is possible that he may develop FTD in the future, as his family history has revealed 9 out of 12 affected individuals with FTD, presenting at an average age of 60.6 years in 6 individuals.

Neuromuscular evaluation revealed normal muscle strength testing but mild scapular winging, normal CKs, normal EMG and normal spirometry. However, muscle biopsy obtained of the vastis lateralis muscle revealed changes consistent with inclusion body myopathy with rare rimmed vacuoles present in several foci of atrophic fibers on H&E staining (Fig. 1b). Further ultrastructual examination showed intra-fiber inclusions containing amorphous debris, myelin figures and tubovesicular material again consistent with inclusion body myopathy. Although complete details are lacking, the average age of onset of IBM in 9 out of 12 affected individuals is 56.8 years.

There was no evidence for Paget's Disease of bone with normal alkaline phosphotase levels and radionuclide scans, and in fact the only case of Paget's Disease within the family was introduced through marriage (Individual III:7).

2. Discussion

Although most cases of PD are thought to be sporadic, 5% do have a familial etiology. More than 15 loci and 11 causative genes have been identified and are involved in mitochondrial function, the ubiquitin–proteasomal system, autophagy/lysosomal pathways and membrane trafficking.

VCP is involved in a wide variety of cellular functions including cell cycle control/apoptosis, ubiquitin dependent endoplasmic reticulum-associated protein degradation (ERAD), autophagy/lysosomal activity, stress responses, membrane fusion, nuclear envelope reconstruction and post mitotic Golgi reassembly. Mutations in the VCP gene primarily affecting its ubiquitin binding domain result in IBMPFD [2]. Neuropathology has demonstrated ubiquitin- and TDP-43 positive inclusions but no Lewy Bodies [3]. Bersano et al. [4] reported an Italian male with IBM followed several years later, by FTD, with an R159C mutation. Interestingly the R159C mutation appears to be protective for Paget disease of bone since no individual has exhibited this feature.

We present the first case of a patient presenting with typical PD associated with a VCP gene mutation. The incidence of PD in IBMPFD may be potentially underestimated as additional cases of parkinsonism have been observed in subjects from our families (unpublished observations), however, these patients were suffering from end stages of dementia and formal PD evaluations on them are not available. Additionally Spina et al. have reported individuals with PD [5], however complete details are lacking. We cannot be certain that the mutation is causative in this single case report, but given hypothesized pathogenic processes of PD and IBMPFD, further investigation of their association deserves investigation. The present case adds to the increasing body of literature identifying

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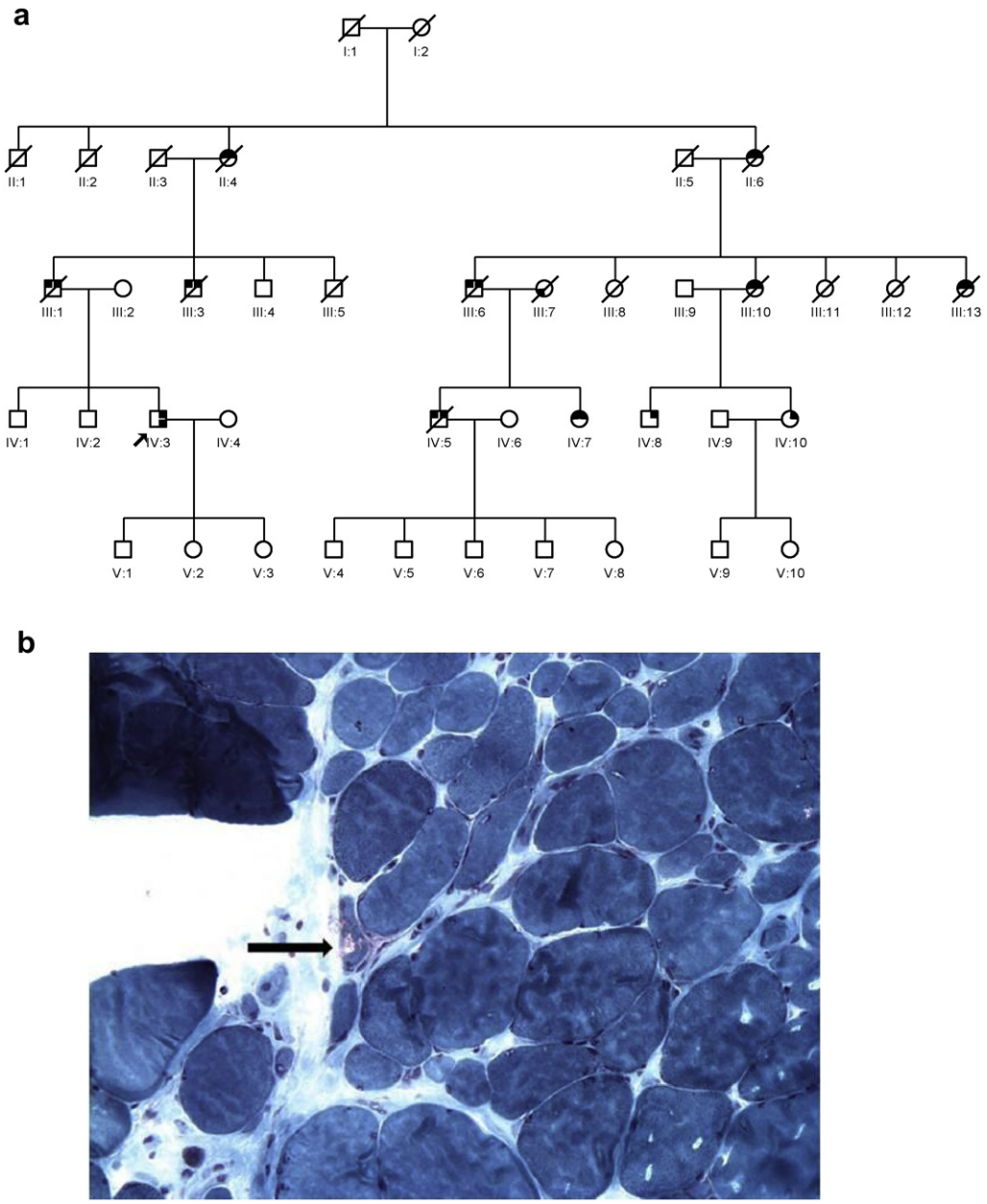

Fig. 1. a. The marked individuals in Family 1 and Family 2 represent those affected with IBMPFD. The location of the shading in the diagram represents the different manifestations of the disease. Upper left = expression of frontotemporal dementia, lower left = Paget disease of the bone introduced into the family, upper right = inclusion body myopathy, lower right = Parkinson's disease. b. Muscle Biopsy of Vastus lateralis (10X Gomori Trichrome) – moderate fiber size variation with rare atrophic muscle fibers containing rimmed vacuoles (black arrow).

Table 1
Clinical data of affected individuals.

Pedigree No. (Family 1 $N = 13$)	Age (years)	Deceased	Sex	PDB	IBM	FTD	Age DX PDB (years)	Age DX IBM (years)	Age DX FTD (years)	Parkinson's disease
II:4	79	+	F	–	+	+	–	60	66	–
II:6	71	+	F	–	+	+	–	–	–	–
III:1	69	+	M	–	+	+	–	57	64	–
III:3	69	+	F	–	+	+	–	59	63	–
III:6	62	+	M	–	+	+	–	–	–	–
III:7	85	+	F	+	–	–	–	–	–	–
III:10	82	+	F	–	+	+	–	–	–	–
III:13	75	+	F	–	+	+	–	60	65	–
IV:3	55	–	M	–	+	–	–	49	46	+
IV:5	63	+	M	–	+	+	–	53	60	–
IV:7	67	–	F	–	+	+	–	59	–	–
IV:8	66	–	M	–	+	–	–	60	–	–
IV:10	59	–	F	–	+	–	–	55	–	–
Mean	69.38	9	8F/5M	1	12	9	–	56.88	60.66	1

genetic factors associated with PD, and classic L-dopa-responsive PD may be added to the potential consequences of VCP mutations.

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