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Distinct distal myopathy phenotype caused by *VCP* gene mutation in a Finnish family

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Abstract

Inclusion body myopathy with Paget disease and frontotemporal dementia (IBMPFD) is caused by mutations in the valosin-containing protein (VCP) gene. We report a new distal phenotype caused by *VCP* gene mutation in a Finnish family with nine affected members in three generations. Patients had onset of distal leg muscle weakness and atrophy in the anterior compartment muscles after age 35, which caused a foot drop at age 50. None of the siblings had scapular winging, proximal myopathy, cardiomyopathy or respiratory problems during long-term follow-up. Three distal myopathy patients developed rapidly progressive dementia, became bedridden and died of cachexia and pneumonia and *VCP* gene mutation P137L (c.410C > T) was then identified in the family. Late onset autosomal dominant distal myopathy with rimmed vacuolar muscle pathology was not sufficient for exact diagnosis in this family until late-occurring dementia provided the clue for molecular diagnosis. VCP needs to be considered in the differential diagnostic work-up in patients with distal myopathy phenotype.

Keywords: Distal myopathy; Frontotemporal dementia; Valosin-containing protein

1. Introduction

Mutations in the valosin-containing protein (VCP) gene cause inclusion body myopathy with early-onset Paget disease and frontotemporal dementia (IBMPFD) [1]. This progressive autosomal dominant disorder is characterized by variable penetrance of its three main features: myopathy, Paget disease and dementia [1]. VCP has a role in multiple cellular processes, including endoplasmic reticulum associated degradation (ERAD) and proteasome-mediated protein degradation [2–4]. Recent data show that VCP has an essential role also in autophagy suggesting that impaired autophagy might contribute to the pathogenesis of IBMPFD [5,6]. Of the 19 reported *VCP* gene mutations the most common is R155H [7]. It has been shown to increase ubiquitin-conjugated proteins, impair degradation of ERAD substrates and increase aggregation of VCP [8]. Histopathology of the myopathy is characterized by rimmed vacuoles and occasional cytoplasmic VCP- and ubiquitin-positive inclusions [9,10]. Typical features of dementia have consisted of behavioral alteration, language dysfunction and relative preservation of memory [10]. In patients with Paget disease clinical symptoms have included pathological fractures, bone deformity, spine or

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hip pain with elevated levels of serum alkaline phosphatase (ALP) [10].

The clinical muscle phenotype of IBMPFD typically consists of late adult onset proximal upper and lower limb weakness with frequent axial myopathy, scapular winging, and variable involvement of distal muscles. Respiratory failure and cardiomyopathy have also been encountered in several patients [10–12]. In this report we describe a family with a late-onset pure distal manifestation of the myopathy, which caused the patients to be first diagnosed with Welander distal myopathy or tibial muscular dystrophy (TMD, Udd myopathy), until the correct genetic diagnosis was established.

2. Patients and methods

We describe a Finnish family with nine affected patients in three generations (Fig. 1). The patients in the previous generations had already died when examinations started. The current generation consisted of nine siblings, of whom one died in an accident at the age of 19. The other eight siblings and their father were clinically and genetically examined and followed-up over more than a decade. They underwent electrophysiological examinations with nerve conduction velocity (NCV) studies and electromyogram (EMG), muscle biopsy, creatine kinase (CK) measurement and muscle imaging by computed tomography (CT) or magnetic resonance imaging (MRI) when possible. Some of them also had neuropsychological evaluation and screening for Paget disease by radiological examinations of the skull, long bones and measurement of ALP. The study was approved by the Institutional Review Board of Tampere University Hospital and performed in accord with the Helsinki declaration.

2.1. Muscle biopsy

Tibialis anterior muscle biopsies were obtained from three patients (III-1, III-3 and III-5). Two patients underwent a second biopsy from peroneus longus muscle (III-5) and from tibialis posterior muscle (III-3). Samples were snap frozen and 8–10 μm sections were cut and examined by using standard histochemical stainings including hematoxylin and eosin, modified gomori trichrome, reduced nicotinamide adenine dinucleotide-tetrazolium reductase (NADH-TR) and ATPase at pH 10.4, pH 4.6. For immunohistochemistry antibodies against the following proteins were used: beta-amyloid, ubiquitin, TDP-43, p62, SMI-31, VCP, myosin fast, myosin slow, dystrophin 1-3, desmin, myotilin, alpha B-Crystallin, developmental and neonatal myosin heavy chain.

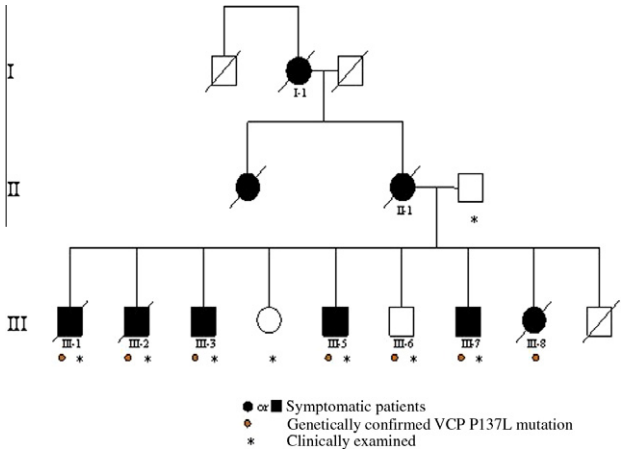

Fig. 1. Pedigree of the family.

2.2. Genetic analysis

Blood samples of all siblings in generation III and their father were obtained and DNA was extracted by standard methods. Haplotype genotyping for the founder mutation haplotypes of Finnish TMD on chromosome 2q31 and the Nordic Welander disease locus on 2p13 were performed. Exons 3–6 (in some patients only exon 4) and their flanking regions of *VCP* gene were amplified by PCR, sequenced and analyzed (ABI 3130 Genetic Analyzer, Applied Biosystems, Foster City, CA) using standard protocols. Exon 4 was also sequenced in 158 normal control chromosomes.

3. Results

In three generations, there were nine affected patients, two in the past generation without genetic testing and seven out of nine siblings in the generation examined (Table 1). The siblings' aunt became wheelchair-bound at the age of 70 without known cause. She had also dementia since the age of 65 and was probably affected by the same disease. Patients in generation III had onset of distal leg muscle weakness and atrophy in the anterior compartment after age 35, which caused a foot drop at the age of 50 (Fig. 2). The oldest brother (III-1) also had marked atrophy and myopathic EMG findings of small hand muscles at age 38; this caused him first to be diagnosed with Welander distal myopathy. The second oldest of the siblings (III-2) had poliomyelitis when he was 9 months old and was left with paralysis of the left leg and weakness of the hands. He was stable and could walk with a stick until the age of 50. Since then progressive distal myopathy resulted in a loss of ambulation and a rapidly progressive dementia developed at the age of 60. Two siblings, III-3 and III-5, did not have any upper limb involvement and they were clinically diagnosed with TMD. None of the siblings had scapular winging, proximal myopathy, cardiomyopathy or respiratory problems during the follow-up. CK values were normal or slightly elevated.

Microscopic changes in muscle biopsies were predominantly myopathic and most pronounced in biopsies obtained from tibialis anterior muscles, which all showed rimmed vacuolar changes. Endomysial fibrosis as well as atrophic and hypertrophic fibers with splitting and internal