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One family, one gene and three phenotypes: A novel *VCP* (valosin-containing protein) mutation associated with myopathy with rimmed vacuoles, amyotrophic lateral sclerosis and frontotemporal dementia

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ABSTRACT

Background: VCP (valosin-containing protein gene) variants have been associated with peripheral and central neurodegenerative processes, including inclusion body myopathy (IBM), Paget disease of bone (PDB), frontotemporal dementia (FTD), and familial amyotrophic lateral sclerosis (ALS) type 14. The combination of IBM, PDB (IBMPFD1) can presented in one individual. However, the association of IBMPFD1 and ALS in the same family is rare.

Methods: We reported three individuals from a Brazilian kindred with intrafamilial phenotype variability. Whole exome sequencing (WES) of the proband was performed and revealed a novel *VCP* variant. *VCP* Sanger sequencing was performed in the proband and his family members to confirm WES finding and segregation. We performed a systematic review of the literature regarding the genotypic-phenotypic *VCP* correlations.

Results: Each individual presented with either myopathy with rimmed vacuoles, ALS, or FTD. There was no PDB. WES of the proband identified the heterozygous variant c.271A > T (p.Asn91Tyr) in the exon 3 of *VCP*. Sanger sequencing confirmed the segregation of this variant in an autosomal-dominant pattern.

Conclusion: This study expands the genotypic spectrum of the missense mutations of the *VCP* gene with a novel p.Asn91Tyr variant found in a Brazilian family presenting with the unusual intrafamiliar association of myopathy with rimmed vacuoles, ALS and FTD.

1. Introduction

Valosin-containing protein (VCP, also known as *CDC48* or homolog of *p97*) is an ubiquitously expressed, multifunctional member of AAA (ATPase Associated with diverse cellular Activities) superfamily and has been involved with multiple ubiquitin-dependent intracellular processes [1–4]. Autosomal dominant, heterozygous missense variants in *VCP* are linked to a spectrum of phenotypes (also known as Multisystem Proteinopathy) which includes myopathy with rimmed vacuoles or inclusion body myopathy (IBM), early-onset Paget disease of the bone (PDB), frontotemporal dementia (FTD) or familial amyotrophic lateral sclerosis (ALS type 14, OMIM #613954) [1,5,6].

VCP-related myopathy with rimmed vacuoles, PDB or FTD in any combination is known as IBMPFD1 (OMIM #167320), an autosomal dominant inherited spectrum of disorders with incomplete penetrance and adult onset [7]. Myopathy is the most common feature, characterized by progressive proximal-predominant muscle weakness resembling a limb-girdle muscular dystrophy pattern, along with normal or mildly elevated serum creatine kinase (CK) levels [8]. A distal myopathy phenotype has also been reported [9]. The most common findings in the muscle biopsy are rimmed vacuoles and ubiquitin-positive, VCP-positive and TDP-43-positive inclusions [8,10]. PDB is seen in approximately 50% of cases and presents with osteolytic bone lesions or polyostotic skeletal disorganization, pathological fractures, and high serum alkaline phosphatase (ALP) [3,8,10]. FTD is recognized in almost one third of

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patients harboring *VCP* pathogenic variants. Neuroimaging studies have shown frontal and anterior temporal lobe cortical atrophy [8,10,11]. The first Brazilian family with IBMPFD1 harboring p.Arg93Cys variant at *VCP* was described in 2011 [11].

Other neurological features have also been described, such as parkinsonism, dystonia, myotonia, sensorimotor axonal neuropathy and sensorineural hearing loss [3,10,12]. Systemic features have been rarely reported, such as cardiomyopathy, cataracts and hepatic steatosis, but the association of these systemic manifestations with *VCP* mutations remains uncertain [3].

Herein, we describe three Brazilian patients from the same family presenting with isolated IBM-like myopathy (proband), sporadic ALS (his brother) and isolated late-onset FTD (his father) harboring a novel *VCP* variant. No PDB was seen. To our knowledge, this is first description of intrafamilial association of ALS, myopathy and FTD in a Brazilian kindred.

2. Patients and methods

2.1. Patients

This study was approved by UNIFESP Research Ethics Board. An informed consent was obtained from all subjects or their legal representatives. The proband, his brother and his father (Fig. 1A) were clinically assessed and medical records were reviewed, including results of neuroimaging, serum CK and ALP levels, nerve conduction studies (NCS)/needle electromyography (EMG), and muscle biopsy whenever available.

2.2. Muscle biopsy

Open muscle biopsy was performed in the left vastus lateralis of the proband under local anesthesia. The collected fragments were snap-frozen in isopentane and cooled in liquid nitrogen for further analysis. The muscle fragments underwent the following routine stains: hematoxylin and eosin (HE), modified Gomori trichrome, periodic acid-Schiff (PAS) and oil red O, and alkaline phosphatase. In addition, we processed for standard biochemical reaction for cytochrome oxidase (COX), nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR), succinate dehydrogenase (SDH), and myofibrillar ATPase at pH 9.4, 4.3 and 4.6. Immunohistochemistry for dystrophin, sarcoglycans, dysferlin, merosin, desmin and caveolin 3 was also performed. In addition, we tested markers for macrophages (CD68), lymphocytes (CD4+ and CD8+) and major histocompatibility complex class I (MHC-I).

2.3. Genetic analysis

Whole exome sequencing (WES) of a DNA sample of the proband's peripheral blood cells was performed at Mendelics Genomic Analysis

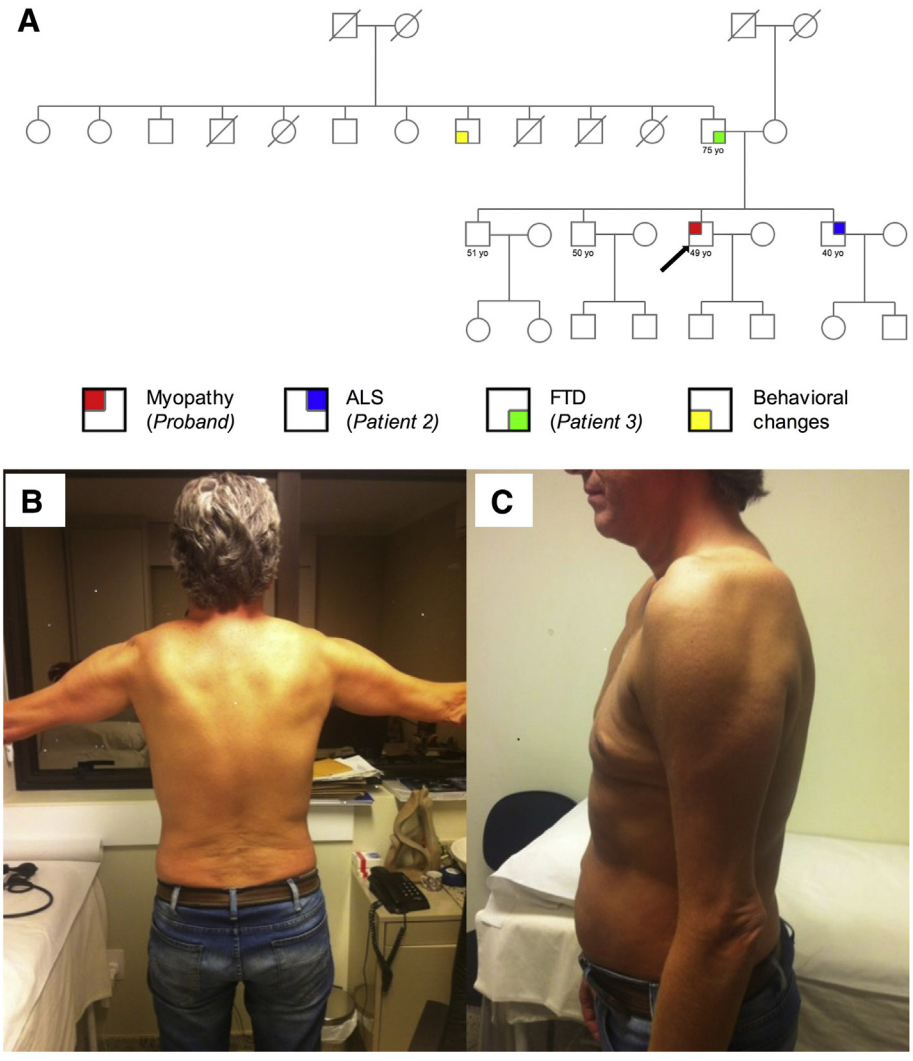

Fig. 1. (A) Pedigree of the Brazilian kindred disclosing a novel autosomal dominant *VCP* variant linked to different phenotypes. (B) and (C) proband examination showing mild scapular winging and reduced deltoid muscle bulk.