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Mutations in the p97 gene cause familial inclusion body myopathy associated with Paget disease of the bone and frontotemporal dementia. *G.D.J. Watts[1], J. Wymer[1], S. Mehta[1], S. Mumm[2], M. Whyte[2], A. Pestronk[3], D. Darvish[4], V.E. kimonis[1]*. 1) Division of Genetics, Children's Hospital Boston, Harvard Medical School, Boston, MA; 2) Division of Bone and Mineral Diseases, Washington University School of Medicine and Barnes-Jewish Hospital Research Institute, St. Louis MO; 3) Department of Neurology, Washington Univ. School of Med., St Louis, MO; 4) HIBM Research Group, 16661 Ventura Blvd., #311, Encino, CA.

We report, in 9 families, molecular findings for a new autosomal dominant disorder associated with inclusion body myopathy clinically resembling limb girdle muscular dystrophy, Paget disease of bone in the majority and frontotemporal dementia in a third of individuals. The critical locus for this unique disorder termed IBMPFD (MIM 605382) on 9p21.1-p12, spans 5.5Mb. This is a gene rich locus and encompasses two other myopathies; autosomal recessive inclusion body myopathy (IBM2) and a rare nemaline myopathy. We have identified five missense mutations within the p97 gene in 9 families with IBMPFD. p97, which is also referred to as CDC48 and VCP (Valosin Containing Protein), is widely expressed and contains two AAA ATPase domains. The p97 protein has been implicated in two distinct and crucial cell pathways, namely membrane biogenesis and targeted protein degradation. The mutations associated with IBMPFD were found to cluster in the N-domain and potentially define a new domain having a critical role in skeletal muscle, osteoclasts, frontal and anterior temporal lobe function.

With growing evidence for disruption of the ubiquitin pathway being involved in the pathological effects for muscle (limb-girdle muscular dystrophy 2H: TRIM32), Paget (Sequestosome 1) and neurodegenerative disease such as CMT1C, mutations in VCP may account for a significant proportion of patients with isolated myopathy, Paget disease of bone and frontotemporal dementia and may define a new ubiquitin-based mechanism of regeneration/stress response leading to inclusion body formation.