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### Authors
Weihl, C
Miller, S
Pestronk, A
et al.



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**G.P.13.04**

**IBMPFD mutations in p97/*VCP* cause the accumulation of ubiquitinated proteins via impairment in the ubiquitin-proteasome pathway**

Weihl, C. [1,*]; Miller, S. [1]; Pestronk, A. [1]; Hanson, P. [2]; Watts, G. [3]; Kimonis, V. [4]

[1] *Washington University School of Medicine, Neurology, Saint Louis, Missouri, United States;* [2] *Washington University School of Medicine, Department of Cell Biology and Physiology, Saint Louis, Missouri, United States;* [3] *Boston Children's Hospital, Genetics, Boston, Massachusetts, United States;* [4] *University of California-Irvine, Genetics, Irvine, California, United States*

Mutations in *VCP* cause the multisystem disorder inclusion body myopathy (IBM) with Paget's disease and frontotemporal dementia (IBMPFD). *VCP* is involved in many cellular pathways; most notably the ubiquitin proteasome pathway (UPP). Mutations in VCP may affect this pathway. We explored the mechanism by which *VCP* leads to IBM using patient tissue, cell culture and a transgenic animal. Histochemical examination of 9 IBMPFD patient muscle biopsies (4 families; 2 mutations) reveals that 7/9 contained rimmed vacuoles while all had evidence of ubiquitinated and VCP inclusions. These inclusions were myonuclear and sarcoplasmic in location. We generated tetracycline inducible cell lines that express VCP-WT, dominant negative VCP or several IBMPFD mutant VCP proteins. These cells express exogenous VCP at 1–2 times the level of endogenous VCP. Remarkably, IBMPFD mutant VCP expressing cells have a dramatic increase in ubiquitinated proteins as measured by immunofluorescence and Western blot. This finding is similar to the expression of a dominant negative VCP protein. IBMPFD mutant expressing cells fail to degrade a UPP reporter and are more sensitive to proteasome inhibition as measured by cell death assays. Transgenic expression of IBMPFD mutant VCP R155H in the skeletal muscle of mice results in animal weakness that begins at ~6 months of age. Consistent with our patient and cell culture data, these animals have an increase in ubiquitinated protein inclusions as compared with VCP-WT control animals. The increase in ubiquitinated proteins may be due to a reduction in the activity of the 20S proteasome in these animals. We suggest that IBMPFD mutations in *VCP* lead to a perturbation in the UPP resulting in the accumulation of undegraded ubiquitinated proteins, myopathic changes and muscle weakness. This study lends insight into the pathogenesis of IBMPFD as well as other hIBMs and the more common sporadic IBM.

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