LETTER TO THE EDITOR

Reply: Hereditary spastic paraplegia caused by a mutation in the VCP gene
VCP: A Jack of all trades in neuro- and myodegeneration?

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Sir, de Bot et al. report on a novel autosomal-dominant form of hereditary spastic paraplegia due to a valosin-containing protein (VCP) missense mutation. Mutations of the human VCP gene on chromosome 9p13.3 have previously been described to cause IBMPFD (inclusion body myopathy with early onset Paget’s disease of bone and frontotemporal dementia, OMIM #167320) (for current review on IBMPFD see Nalbandian et al., 2011) and ALS14 (amyotrophic lateral sclerosis with or without frontotemporal dementia, OMIM #613954) (for current review on ALS see de Carvalho and Swash, 2011).

In the light of the complexity of VCP’s multiple cellular functions, dissecting the molecular pathogenesis of these three diseases is a true scientific challenge. VCP is a ubiquitously expressed, abundant and evolutionarily highly conserved member of the type II AAA-ATPase family (ATPases associated with a wide variety of cellular activities). The targeted ablation of VCP in mouse as well as of its orthologue in fruit fly, yeast and a protist is a lethal event (Frohlich et al., 1991; Leon and McKearin, 1999; Lamb et al., 2001; Müller et al., 2007). VCP plays essential roles in a wide variety of cellular processes comprising nuclear envelope reconstruction, cell cycle, post-mitotic Golgi reassembly, suppression of apoptosis, DNA damage response and endocytosis. In addition, VCP has been attributed to exert central roles in several protein quality control pathways (for review of the multiple functions of VCP refer to Yamanaka et al., 2012).

The pathological consequences of VCP missense mutations have thus far primarily been studied in the context of IBMPFD. Within the large group of human protein aggregation diseases, IBMPFD has a unique role, because VCP- and ubiquitin-positive pathological protein aggregates are present in both neuronal and striated muscle cells (Schröder et al., 2005; Hübbers et al., 2007). However, VCP-positive inclusions are not specific for IBMPFD and have been documented in a wide variety of other neuro- and myo-degenerative disorders comprising Parkinson’s disease, Lewy Body disease, Huntington’s disease, amyotrophic lateral sclerosis, spinocerebellar ataxia type III (Hirabayashi et al., 2001; Mizuno et al., 2003; Nan et al., 2005) and myofibrillar myopathies (own unpublished data). As key events in IBMPFD-related pathogenesis, several studies emphasize that mutant VCP inflicts deleterious and multi-scale effects on cellular protein quality control which is essential for the removal of mis-folded and degradation-prone proteins. In particular, mutant VCP has been attributed to hamper endoplasmic reticulum-associated protein degradation, proteasomal protein degradation, autophagosome maturation, endosomal trafficking and lysosomal protein degradation (Wang et al., 2004; Ju and Weihl, 2010; Bug and Meyer, 2012). The intriguing role of VCP in neurodegeneration is further highlighted by the observation that the amount of VCP protein expression modulates protein aggregation and neurotoxicity (Böddrich et al., 2006).

The present report by de Bot and colleagues provides a further pathogenic link between VCP-related protein aggregation pathology and motor neuron diseases. Though pathological protein aggregates have been described in motor neurons of patients with amyotrophic lateral sclerosis, no such data are currently available for VCP-related amyotrophic lateral sclerosis and hereditary spastic paraplegia. The authors identified the p.Arg159Cys VCP missense mutation in two index patients from one family with the unusual clinical presentation of spastic paraplegia in...
combination with Paget’s disease of bone. Cognitive function was reported to be normal and there were no sensory, extrapyramidal and cerebellar signs, and no sphincter disturbances. However, one sibling had fascination and EMG showed evidence of lower motor neuron involvement in two regions. Paget’s disease of bone and gait problems were also reported in two other siblings and their father. Though the documented upper and lower motor neuron involvement is basically in keeping with the diagnosis of possible amyotrophic lateral sclerosis, the authors argue that the clinical presentation and the disease course are more in favour with the diagnosis of hereditary spastic paraplegia (Dion et al., 2009; Schüle and Schöls, 2011). In this context, it should be noted that evidence of peripheral sensory and motor nervous system involvement has been described in a subset of patients with IBMPFD (Miller et al., 2009).

With regard to the pathogenicity of the here reported hereditary spastic paraplegia causing p.Arg159Cys VCP mutation, it is of interest that this particular mutation has previously been described in a patient with IBMPFD (Bersano et al., 2009). In addition, another missense mutation of the same codon, p.Arg159His, has been detected in patients with IBMPFD from four unrelated families (Haubenberger et al., 2005; van der Zee et al., 2009). Yet another genetic alteration of this codon, p.Arg159Gly, was reported in the context of amyotrophic lateral sclerosis with or without frontotemporal dementia (Johnson et al., 2010). The latter study further described three more ALS14 causing VCP mutations, p.Arg155His, p.Arg191Gln and p.Asp592Asn. Two of these, p.Arg155His and p.Arg191Gln, have also been reported in patients with IBMPFD (Watts et al., 2004; Hübbers et al., 2007).

Beyond a mere clinico-genetic association, the study by de Bot et al. strongly corroborates a molecular link between VCP and motor neuron diseases. VCP was found to directly interact with strumpellin (KIAA0196) (Clemen et al., 2010), which in its mutant form causes a severe and relatively pure motor form of adult-onset hereditary spastic paraplegia (SPG8, OMIM #603563) (Valdmanis et al., 2007). Both proteins are components of a high molecular weight protein complex with an estimated molecular mass of 2.5 MDa (Clemen et al., 2010). In addition to a direct molecular interaction, the expression levels of VCP and strumpellin seem to be inter-related. In our VCP haploinsufficient mouse model the strumpellin messenger RNA and protein expression levels were significantly upregulated (Fig. 1; mouse model to be published elsewhere). Furthermore, strumpellin has been identified as a component of the evolutionarily highly conserved 550 kDa WASH (Wiskott Aldrich Syndrome protein and SCAR homologue) complex which modulates Arp2/3-mediated actin polymerization (Derivery et al., 2009; Jia et al., 2010). Intriguingly, the reduced levels of VCP also seem to influence the pattern of 6 out of the 7 WASH complex subunits, i.e. WASH1 itself, strumpellin, SWIP (Strumpellin and WASH interacting protein, previously known as KIAA1033), FAM21C, CapZα1, CapZβ, and CCDC53 (Fig. 1). The neurobiological relevance of this protein complex is further highlighted by the observation that mutations in the WASH complex subunit SWIP have been attributed to cause familial autosomal recessive intellectual disability (ARID) (Ropers et al., 2011).

Is there further evidence of a functional relationship between VCP and the WASH complex? Indeed, our dot-blot overlay and pull-down experiments employing recombinant purified proteins demonstrated a direct interaction between VCP and SWIP as well as strumpellin and SWIP (to be published elsewhere). Moreover, VCP and the WASH complex have both been implicated to play a role in endosomal trafficking (Derivery et al., 2009; Ritz et al., 2011). The assumption that VCP and strumpellin-related hereditary spastic paraplegias are caused by defects in membrane trafficking, a cellular process that has been implicated in other genetic forms of hereditary spastic paraplegia (Dion et al., 2009), certainly has its appeal. Are disturbances in a macromolecular complex formed by hexameric VCP and the WASH complex the common denominator of hereditary spastic paraplegia, amyotrophic lateral sclerosis, IBMPFD and ARID pathogenesis? Is the marked phenotypic variability of VCP diseases related to functional alterations of this protein complex? In this line of thinking, mutations in VCP, strumpellin or other members of the WASH complex

![Figure 1](https://academic.oup.com/brain/article-abstract/135/12/e224/282985)  
**Figure 1** VCP and WASH complex expression pattern in a VCP haploinsufficient mouse strain. **Left**: Note the decreased VCP protein expression (rabbit polyclonal, Novus Biologicals NB100-1557) in conjunction with increased strumpellin protein expression (rabbit polyclonal EP083578/SY1593) (Clemen et al., 2010) in total protein extract preparations from skeletal muscle tissue derived from wild-type (WT) and VCP haploinsufficient (HEM) littermates. GAPDH was used as an internal loading control (not shown). **Right**: Quantitative real-time PCR analyses of VCP and WASH complex subunit messenger RNA levels in skeletal muscle tissue derived from the same mice. Note that the messenger RNA levels of 6 out of 7 WASH complex components are upregulated. GAPDH messenger RNA levels were used for normalization and ratios of HEM to WT were calculated. Mean values and standard errors were obtained from two experiments (four measurements each) of two animals per genotype.
may cause further rare forms of motor neuron or protein aggre-
gate diseases. Since VCP seems to be a ‘Jack of all trades’ in
neuro- and myo-degeneration, a closer look at its molecular inter-
action partners may unravel the pathogenesis of these disorders.

Acknowledgements

We are grateful to Mr Jan Matthias, Ms Maria Stumpf and
Dr Karthikeyan Tangavelou (University of Cologne, Germany) as
well as Dr Johanna Schütz and Dr Karl-Heinz Strohbeck
(University Hospital Erlangen, Germany) for their support in this
project.

Funding

Our work on VCP is funded by the German Research Foundation
(DFG/FOR1228: CL 381/3-1, EI 399/5-1, SCHR 562/9-1), the
Fritz-Thyssen-Foundation (10.07.1.165) and the Tom-Wahlig-
Foundation.

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