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Valosin-Containing Protein (VCP) Disease and Familial Alzheimer's Disease: Contrasts and Overlaps

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1. Introduction

Contrasts between two entities may be illuminating because of the emphasis on what each is not. Here we describe two proteinopathies producing brain neurodegeneration in mature adults, autosomal dominant valosin-containing protein (VCP) disease and Familial Alzheimer's disease (FAD) caused by presenillin-1 (PSEN1) mutations, illustrating both contrasting patterns of clinical presentation and known neuropathologic and imaging features, and points of congruence.

Mutations primarily in the ubiquitin binding domain of the VCP gene cause frontotemporal dementia as part of a rare but important disorder that also encompasses inclusion body myopathy, Paget disease of bone, and in some cases, motor neuron disease. The VCP dementia has onset in the 50s, characterized by abulia, expressive language loss, and executive dysfunction. The pattern of degeneration generally is anterior, in frontal and temporal lobes, involving neuronal nuclear inclusions of ubiquitin and TAR DNA binding protein 43 (TDP-43), but not amyloid or tau.

The most common mutations causing FAD occur in the PSEN1 gene. The associated dementia has onset in the late 40s, characterized by early memory loss and diffuse amyloid vasculopathy, and posteriorly distributed neuritic amyloid plaque and neurofibrillary tau pathology in medial temporal and parietal lobes, but not ubiquitin or TDP-43. Nonetheless, both VCP and PSEN1 pathologies have extensively documented abnormalities in similar protein processing pathways.

2. VCP Disease – IBMPFD

Hereditary inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia (IBMPFD; OMIM 167320) is a unique and rare disorder associated with mutations primarily in the ubiquitin binding domain of the valosin-containing protein

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(VCP) gene (Watts et al. 2003; Watts et al. 2004). VCP, a member of the AAA-ATPase super-family, occupies the crossroads of many cellular functions including ubiquitin mediated protein degradation, cell cycle control, membrane fusion, and golgi reassembly (Kimonis and Watts 2005; Halawani and Latterich 2006). It is lethal as a homozygous deletion in mice (Muller et al. 2007), and an important regulator of neuronal and dendritic development (Rumpf et al. 2011).

Current theories concerning the pathogenesis of VCP disease include altered protein degradation via the ubiquitin-protosomal system (Kakizuka 2008; Dai and Li 2001; Wojcik, Yano, and DeMartino 2004), generalized endoplasmic reticulum (ER) dysfunction with altered protein trafficking (Weihl et al. 2006; Wojcik et al. 2006; Poksay et al. 2011), and combined activation and failure of inhibition of cell death pathways (Braun and Zischka 2008). Recently VCP has been implicated in the autophagy/lysosome process (Badadani et al. 2010; Ju et al. 2009; Ju et al. 2008; Ju and Weihl 2010a, 2010b; Tresse et al. 2010). These studies have suggested that VCP mutations cause failure of autophagosome fusion with lysosomes, resulting in accumulation of ubiquitin together with other autophagosome proteins LC3 and p62/sequestosome, in rimmed vacuoles, a hallmark of VCP muscle disease (Vesa et al. 2009, Ju et al. 2009; Tresse et al. 2010).

Certain mutations are also suspected to interrupt the integrity of the hexomeric ring structure of the active VCP complex (Halawani et al. 2009), and its interaction with its adaptors, e.g. p47, gp78 and Npl4-Ufd1 (Alzayady et al. 2005), although this finding has not been universally replicated (Weihl et al. 2007). Our group has confirmed that mutant VCP protein exhibit strongly altered co-factor interactions suggesting that imbalanced co-factor binding to p97 is a key pathological feature of IBMPFD and potentially of other proteinopathies involving VCP (Fernandez-Saiz and Buchberger 2010). Elevated ATPase activity associated with cellular protein mislocalization (Manno et al. 2010) is associated with VCP mutations. Recently studies revealed significant reduction in ATP level in hs.TER94A229E and hs.TER94R188Q drosophila models which may contribute to the neurodegeneration phenotype (Chang et al. 2011, Ritson et al. 2010).

The R155H VCP knock-in heterozygous mouse is a promising model demonstrating several typical clinical and molecular features of the disease including progressive weakness, vacuolization of myofibrils with centrally located nuclei, and cytoplasmic accumulation of TDP-43 and ubiquitin in brain as well as in myofibers (Badadani et al. 2010; Custer et al. 2010). It may prove to be very useful in translational research studies seeking therapies for VCP disease. Analysis of a Drosophila model has provided evidence that mutant VCP interacts abnormally with TDP-43 as a gain-of-function mechanism to cause redistribution of TDP-43 from its usual location in the nucleus to the cytoplasm (Ritson et al. 2010). These findings would be usefully replicated in the mouse model.

The clinical disorder typically presents in the early 40s with progressive proximal muscle weakness or with Paget disease of bone (PDB). Weakness is associated with rimmed vacuoles and inclusions on muscle biopsy in the majority of individuals; PDB is present in approximately half of affected individuals. Frontotemporal dementia (Table 1) becomes symptomatic later in a third of affected at a mean age of 55 years (Kimonis and Watts 2007; Kimonis, Fulchiero et al. 2008; Kimonis, Mehta et al. 2008; Kimonis and Watts 2005; Kovach et al. 2001). A small percentage of individuals have been identified with motor neuron disease (MND) phenotype (Johnson et al. 2010), Parkinson's disease (Johnson et al. 2010;

Rohrer et al. 2011), cardiomyopathy (Hubbers et al. 2007; Miller et al. 2009), liver disease (Guyant-Marechal et al. 2006), cataracts (Guyant-Marechal et al. 2006), hearing loss (Djamshidian et al. 2009), or corticospinal tract dysfunction (Kumar et al. 2010).

The VCP disease-associated dementia typically presents with frontotemporal phenotypes, e.g., altered social behavior, abulia, executive dysfunction, altered expressive language, and loss of semantic knowledge (Table 1). However, different families carrying the same VCP mutation may have a wide variation in clinical phenotype. For example, some families carrying the R159H VCP mutation may have an apparent high penetrance for the dementia phenotype (frequency 75-100%; van der Zee et al. 2009) but different average ages of onset (46 ±2 vs. 62 ±1 years). Other families with R159H may express high penetrance of PDB and IBM phenotype (100%) but demonstrate relatively low dementia frequency (20%; Haubenberger et al. 2005). The presenting dementia phenotype in R155C VCP may be behavioral variant FTD, an AD-like memory loss, or a non-specific cognitive dysfunction across several domains (Guyant-Marechal et al. 2006).

Some of this variability may have to do with the interest and specialty expertise of the clinics in which affected patients are seen, e.g., increasing the likely detection of FTD in a clinic dedicated to this sometimes difficult to diagnose disorder. The age at which the patient is seen and the length of follow-up will determine the presence and degree of cognitive and behavioral symptoms, and thus the likelihood of meeting criteria for a clinical diagnosis. Early memory symptoms may evolve into a more recognizable behavioral syndrome typical of FTD (Guyant-Marechal et al. 2006; Krause et al. 2007; van der Zee et al. 2009). Relative timing of the symptoms of FTD, PDB and IBM may also influence observed phenotypic frequencies – severe muscle disease with cardiomyopathy and respiratory failure might occur before dementia could be observed. Early dementia symptoms could be misinterpreted as a medical complication of severe respiratory or cardiac illness.

Nonetheless a substantial biologic variability across and within families with the same mutation, and across mutations, is well documented in VCP dementia. Potential explanations for variability are modifier genes, epigenetic mechanisms, and environmental exposures, the latter two possibilities as yet unexplored. A possible modifier gene is apolipoprotein-E. Possession of one or more APOE4 alleles was found to be associated with dementia in VCP disease, and increases risk for sporadic FTD in a dose-dependent manner (Bernardi et al. 2006; Mehta et al. 2007; Rosso et al. 2002). Tau haplotype was not associated with VCP dementia (Mehta et al. 2007), and VCP polymorphisms have not been found to be increased in the general population of patients with sporadic FTD (Schumacher et al. 2009).

Despite variability in clinical presentation, the qualitative pathologic changes are relatively uniform (Table 2). Post-mortem brains of individuals with VCP mutations reveal 75% have findings pathologically classified as frontotemporal lobar dementia ubiquitin type (FTLD-U), with abundant intranuclear ubiquitinated protein inclusions, dystrophic neuritis and rare cytoplasmic ubiquitin-positive inclusions (Forman et al. 2006; Kimonis, Fulchiero et al. 2008). Possible exception to this relative uniformity is the finding of vacuolar change in frontotemporal regions but not intranuclear ubiquitin pathology in three autopsies of R155C VCP mutation patients (Guyant-Marechal et al. 2006). This apparent anomaly may have a technical basis, since two of these subjects had increased frontal lobe ubiquitin immunoreactivity on Western blot.

Intranuclear inclusions of ubiquitin co-localized with TDP-43 are widespread and numerous

Author	Mut.	Dementia	Onset Age (n)	Clinical Dementia Onset	Muscle Disease	Paget Disease	Comments
Gidaro, 2008	R155C	2/3	52 (1)	bvFTD	3/3	1/3	Very mild PDB
Guyant-Marechal, 2006	R155C	7/10	57 (7)	bvFTD (4) AD-type (2) Possible FTD (1)	8/10	3/10	Later mutism in AD-type patients; myotonia 7/9; seizure/myoclonus 1/7; liver disease 7/10
Kim, 2011	R155C	3/3	56 (3)	Semantic dementia	2/3	2/3	-
Kalbe, 2011	R155C	-	45	Mild Frontal Impairment	1/1	0/1	Lowered frontal assessment scores
Schroder, 2005	R155C	1/1	47 (1)	Semantic dementia	1/1	0/1	Poor language comprehension and naming, abulia
Miller, 2009	R155H	8/18		bvFTD	18/18	0/18	Cardiomyopathy; sphincter dysfunction
Johnson, 2010	R155H	-	59	Mild Frontal Impairment	1/1	0/1	Lowered frontal assessment scores
Kumar, 2010	R155L	-	-	-	-	-	Corticospinal dysfunction in one
Djamshidian, 2009	G157R	2/4		Mild Frontal Impairment	2/4	4/4	Hearing loss
Bersano, 2009	R159C	1/1	68 (1)	bvFTD	1/1	0/1	No family history; suspected MND plus IBM
Haubenberger, 2005	R159H	0/4	-	No dementia	4/4	4/4	Mild muscle weakness; age >60 4/4
van der Zee, 2009	R159H	10/15	56 (8)	bvFTD (2), possible FTD (2)	5/15	7/15	Early memory, later behavioral in two; three families studied
Johnson, 2010	R191Q	-	50 (1)	Mild Frontal Impairment	4/4	0/4	4/4 ALS; Family history of FTD in two, PDB in one
Watts, 2007	L198W	1/4	50 (1)	Possible FTD	4/4	2/4	Early memory, later behavioral
Rohrer, 2011	I27V	1/2	55 (1)	bvFTD	0/2	2/2	Parkinsonism (1) progressive dysarthria (1)
Guyant-Marechal, 2006	R93C	6/6	58 (6)	bvFTD	3/6	3/6	-
Krause, 2007	R93C	1/1	60 (1)	Semantic dementia	1/1	1/1	Later behavioral syndrome
Guyant Marechault	R93C	6/6	58 (6)	bvFTD	3/6	3/6	-
Watts, 2007	N387H	2/3	46 (2)	bvFTD (1) memory (1)	2/3	0/3	-

Table 1. Dementia in VCP disease. Columns (left to right): 1. Reporting 1st author, 2. Mutation, 3. Number with dementia/ total reported, 4. Average dementia onset age (number reported), 5. Clinical Dementia type (number of each reported), 6. Affected with muscle disease/ total affected, 7. Affected with Paget disease of Bone/ total affected, 8. Additional comments

-			Region Pathology Intensity					TDP-43		VCP								
Author	n	Mut.	Front	Temp	Pariet	Occip	MT	Nu	Cyt	Nu	Cyt	Ubiq	Nfil	tau	aSN	Poly	bAm	Comments
Watts, 2007; Forman, 2006	1	L198W	+	++	-	+/-	++					+	-	-	-	-	-	AHC loss; NFT limbic
Schroder, 2005	1	R155C	++	++	+	+	+/-			+	+	+		-	-		-	Few AT8+tau
van der Zee, 2009	3	R159H	++	++				+				+						"cats-eye" inclusions;
Neumann, 2007; Forman, 2006	1	R155C	+	++	+	+		++		-	-	+		-	-		-	VCP Regional Intensity
Neumann, 2007; Forman, 2006	6	R155H	++	++	++	++	+/-	++	+/-	-	-	+		+/-	-		-	VCP Regional Intensity (4/6)
Guyant-Marechal, 2006	3	R155C	++	++	+					-	-	-		-	-		-	AHC loss, Ubiq. IR 2/3

Table 2. Neuropathology in VCP Disease. Columns (left to right): 1. Reporting 1st author, 2. Number reported, 3. Mutation, 4 - 8. Intensity of regional pathology (subjective, relative, not quantitative); MT – medial temporal), 9-10. TDP-43 Pathology (Nu – intranuclear, Cyt – cytoplasmic), 11-12. VCP Pathology, 13. Ubiquitin staining, 14. Neurofilament staining, 15. Tau Pathology, 16. Alpha-synuclein staining (aSN), 17. Polyglutamine Pathology, 18. Beta-amyloid staining, 19. Additional comments (AHC – anterior horn cell).

in cortical and basal ganglia, sometimes with a "cats-eye" curvilinear morphology (Neumann et al. 2007; Neumann, Tolnay, and Mackenzie 2009). Dystrophic neurites and cytoplasmic inclusions are relatively low in number in VCP disease brain and contain both proteins. TDP-43 appears to be depleted in normal neuronal nuclei (Neumann et al. 2007). The distribution of protein pathology and neuronal loss may be diffuse and include the occipital lobe, but when focal is predominant in the frontal and temporal regions, sometimes asymmetrically to right or left. The medial temporal lobe, particularly the dentate gyrus, is mostly spared. Occasional coexistent tau, alpha-synuclein, or amyloid pathology is detectible in some cases but this is not characteristic. Some authors have reported VCP within inclusions (Schroder et al. 2005), but others have found it only rarely in dystrophic neurites (Forman et al. 2006). Other pathologies, e.g., neurofiliment or polyglutamine, are absent.

TDP-43 has also been identified as the major disease protein in the ubiquitin-positive inclusions of sporadic and familial FTLD-U, including patients with the MND phenotype (Cairns, Neumann et al. 2007). These pathologic features overlap with those of amyotrophic lateral sclerosis. Anterior horn cell loss has been observed on spinal cord examination in some affected subjects with VCP mutations (Liscic et al. 2008), and the MND phenotype has been described as a dominant feature in a family carrying the R191Q VCP mutation (Johnson et al. 2010). In VCP disease, the pathologic classification best fits the description of FTLD-U, type 4 (Sampathu et al. 2006), distinguished by the intracellular localization of the inclusions, relative rarity of cytoplasmic inclusions and dystrophic neurites, and sparing of the medial temporal lobe, particularly the dentate gyrus. The question of whether the neuropathologic features in VCP disease with MND phenotype most resemble FTLD-U type 4 or FTLD-U types 2 and 3 associated with sporadic FTD with MND phenotype, characterized by abundant cytoplasmic inclusions, remains to be answered. Although rare, VCP disease may provide new insight into the molecular mechanism of TDP-43 proteinopathies caused by more common genetic alterations.

Imaging studies of the brain in VCP mutation carriers with cognitive alterations have also demonstrated variability (Table 3). However, few studies have been performed. The variability in part is due to use of differing imaging modalities: structural computed tomography and magnetic resonance imaging, and functional resting fluorodeoxyglucose positron emission tomography (regional glucose uptake; FDG-PET) and single photon emission tomography (regional perfusion; SPECT). These studies have been performed in different combinations and at different stages of cognitive impairment.

Imaging performed in the presence of subtle cognitive changes thought to presage dementia demonstrates no structural change (Kalbe et al 2011; Djamshidian et al 2009; Watts et al. 2007) and occasional subtle regions of glucose hypometabolism (Kalbe et al. 2011). In subjects with dementia, when present local cortical atrophies may be symmetric in the frontotemporal regions (Watts et al. 2007, Miller et al. 2009, Krause et l. 2007, Schroeder et al. 2005, Rohrer et al. 2011, van der Zee et l. 2009) or lateralized to the right or left with an anterior temporal emphasis (Kim et a. 2011). Other structural studies may show only generalized atrophy (Gidaro et al. 2008, Watts et al. 2007, van der Zee et al. 2009, Guyant-Marechal et al. 2006). Hypoperfusion (SPECT) and glucose hypometabolism (FDG-PET) generally correspond to the regions of greatest atrophy seen on structural imaging in the same patients.

Author	Mut	Imaging Modality	Focal Atrophy	Diffuse Atrophy	White Matter	Comments
Gidaro, 2008	R155C	CT	-	(1/1)	-	-
Watts, 2007	N387H	CT	(1/2)	(1/2)	-	"Pick's" diagnosed in one
Watts, 2007	L198W	MR	-	-	-	MR normal; SPECT mild frontal hypoperfusion
Miller, 2009	R155H	MR	(3/3)	-	(3/3)	Frontal atrophy; mild peripheral hyperintensities
Krause, 2007	R93C	MR	(1/1)	-	(1/1)	Severe frontal WM change; PET frontotemporal hypometab.
Schroder, 2005	R155C	MR	(1/1)	-	-	Frontotemporal atrophy
Rohrer, 2011	I27V	MR	(1/2)	-	-	Frontotemporal atrophy, SPECT parietal hypoperfusion
van der Zee, 2009	R159H	MR	(1/1)	-	(1/1)	Frontal and generalized atrophy; SPECT frontotemporal hypoperfusion
van der Zee, 2009	R159H	CT	-	(1/1)	(1/1)	SPECT bifrontal and diffuse hypoperfusion
van der Zee, 2009	R159H	FDG-PET	-	-	-	Frontotemporal hypometabolism
Kim, 2011	R155C	MR (3), FDG-PET (2)	(3/3)	-	(3/3)	Asymmetric frontotemporal atrophy L (2) R (1), corresponding PET hypometabolism in 2. WM change mild, focal.
Guyant-Marechal, 2006	R155C	MR/CT	-	(5/5)	(0/5)	SPECT frontal lobe hypoperfusion (?/5)
Johnson, 2010	R191Q	MR	-	-	-	Normal in (1/1) mild frontal impairment
Djamshidian, 2009	G157R	MR	-		-	Normal (1/1)
Kalbe, 2011	R155C	MR	-	-	-	Pre-dementia; Normal MR and FDG-PET
Kalbe, 2011	R155H	MR	-	-	-	Pre-dementia; Normal MR; FDG-PET hypometabolism L medial temporal (1/1)

Table 3. Imaging in VCP disease. Columns (left to right): 1. Reporting 1st author, 2. Mutation, 3. Modality used, 4. Presence of focal atrophy, (number/ total images reported), 5. Generalized/diffuse atrophy pattern (number/ total images reported), 6. Presence of white matter hyperintensities or other abnormalities (number/ total images reported), 8. Additional comments.

3. Familial Alzheimer's disease-PSEN1

Autosomal dominant familial Alzheimer's disease (FAD; OMIM 104300) is usually of early onset (EOAD; age < 65 years) and has been known for many years (Janssen et al. 2003). Alzheimer's original case description was reported because of the observed early onset of disease at age 51; before then "senile dementia" was thought only to occur in the elderly (Maurer, Volk, and Gerbaldo 1997). Most cases of FAD are attributable to mutation of the PSEN1 gene on chromosome 14 (OMIM 104311; Campion et al. 1999). The remaining cases are found in rare families harboring mutations in amyloid precursor protein (APP) on chromosome 21, in presenillin-2 (PSEN2) on chromosome 1, or with a currently unknown genetic substrate, including overlap with a small part of the Bell curve continuous with late onset AD (LOAD; Brickell et al. 2006).

Here the focus is on PSEN1-related FAD because it is by far the most frequent FAD type and hence more is known about these families. Presenilin-1 is an important component of the gamma-secretase that cleaves amyloid precursor protein (APP) and NOTCH. It is involved in adult neuronal stem cell differentiation (Gadadhar, Marr, and Lazarov 2011), early cortical development (De Gasperi et al. 2008; Wines-Samuelson and Shen 2005), endoplasmic reticulum calcium regulation (Coen and Annaert 2010), and autophagy (Lee et al. 2010). There are currently 194 known PSEN1 mutations (http://www.molgen.ua.ac.be /ADMutations). Nonetheless, wide phynotypic variability has been found across families with PSEN1 mutations, even those harboring an identical putative founder mutation (M146L; Bruni et al. 2010). Individuals with this mutation may demonstrate early memory loss or temporo-spatial disorientation typical of LOAD (58% of 50), but others present with apathy or executive dysfunction (42%). Regardless of clinical manifestations,

neuropathology consists of AD-typical neuritic plaques, neurofibrillary tangles, neuropil threads, and amyloid angiopathy, differing only in the regional distribution of this pathology, a distribution that determines phenotype, e.g., dysexecutive dysfunction is associated with dorsal frontal lobe pathology (Bruni et al. 2010). These observations suggest that a universal intrinsic pattern of molecular profile difference between, for example, frontal and parietal regions will not explain where or in what sequence AD pathology will manifest in persons with M146L PSEN1 mutations.

The spectrum of phenotypic and neuropathologic variation is even wider when different mutations are considered. For example a variant with dementia associated with spastic paraparesis is associated with several PSEN1 mutations: deletion in exon 9, insertion in exon 3, P436Q, R278K, G217R and L85P point mutations, and deletion of codons 83 and 84 in exon 4 (Verkkoniemi et al. 2000; Houlden et al. 2000; Moretti et al. 2004; Ataka et al. 2004; Assini et al. 2003; Smith et al. 2001; Norton et al. 2009). Neuropathology of these variants includes characteristic fluffy spheres of non-neuritic extraneuronal amyloid termed cotton-wool plaques (Houlden et al. 2000). In one patient with a small deletion in PSEN1 exon 12, parkinsonism, spasticity and dementia were the clinical features and neuropathologic examination showed cotton-wool plaques, cortical and subcortical Lewy bodies, and extensive amyloid angiopathy (Ishikawa et al. 2005). Prominent periventricular white matter hyperintensities associated with spastic paraparesis have been observed on MRI in two E280G and in four P284S PSEN1 mutation carriers (O'Riordan et al. 2002; Marrosu et al. 2006). Extensive amyloid angiopathy causing white matter ischemia could explain the paraparesis in these cases.

Clinical studies of PSEN1 mutation kindreds have reported widely variable age of onset, e.g., 28 years in a de novo M233L mutation carrier (Portet et al. 2003) and a range of onset within the same H163T mutation family of 44-65 years (Axelman, Basun, and Lannfelt 1998). Clinical findings can also include, prominent psychiatric symptoms (S170F mutation (Piccini et al. 2007); L392P (Tedde et al. 2000)), a behavioral variant frontotemporal dementia syndrome (bvFTD; L113P(Raux et al. 2000)), anomia (R278I(Godbolt et al. 2004)), seizures and myoclonus (S170F(Snider et al. 2005), cerebellar ataxia, intention tremor, and dysdiadochokinesia. Neuropathologic findings are generally robust depositions in the form of A-beta$_{1\text{-}42(3)}$ and A-beta$_{1\text{-}40}$ amyloid in vessels, sometimes extending into parenchyma and termed dyshoric vasculopathy, neuritic plaques, tau-laden neuropil threads, and hyperphosphorylated tau protein forming intraneuronal tangles within cortical neurons (Janssen et al. 2000; Janssen et al. 2001). Pathologic, brainstem and cortical Lewy bodies (Kaneko et al. 2007; Snider et al. 2005), and possibly Pick-type tauopathy has been found in carriers of the PSEN1 G183V and M146L mutations (Dermaut et al. 2004; Halliday et al. 2005). TDP-43 and ubiquitin are not seen.

A large kindred identified in Columbia, South America is the focus of an ongoing large scale study of AD in its earliest, pre-symptomatic stages, serving as a model for the much more frequent LOAD (>95% of all AD cases; Lopera et al. 1997; Acosta-Baena et al. 2011). The causative mutation is E280A. Onset age in the initial study was an average 47 years, but there was a wide range between 34 and 62 years. The average life span following diagnosis was 8 years (Lopera et al. 1997). Longitudinal follow-up has shown that the earliest detectible cognitive changes occur at average age 35 years, progressing through mild stages of impairment associated with memory complaints to dementia over approximately 15 years. Time from dementia to death is now estimated as 10 years, likely due to improved

methods of early detection and diagnosis as the study has developed (Acosta-Baena et al. 2011). Studies in this kindred using hexamethylpropyleneamine oxime SPECT has demonstrated decreased perfusion in hippocampus, posterior cingulate, and frontoparietal cortex in asymptomatic carriers (n=18) using t-scores based on a template derived from 200 normal subjects. Carriers with diagnosed AD dementia (n=16) had decreased frontal and parietal perfusion compared to normal non-carriers from the same kindred (n=23). The clear major advantages for the study of this kindred is its large size (449 identified mutation carriers), a cognitive phenotype that parallels LOAD, and the very high predictability of dementia in PSEN1 carriers. In contrast, LOAD has no genetic profile or multivariate model that can approach the predictive power of an autosomal dominant mutation.

4. Contrasts and overlaps

At the most general level cortical regions most affected by VCP-associated pathology are connected by the anterior 60% of the corpus callosum and the anterior commissure – the prefrontal, orbitofrontal, premotor and anterior temporal cortices. Anterior horn cells and muscle share the ubiquitin/TDP-43 pathology. Long tract findings are exceptional. The clinical syndromes associated with cortical dysfunction in these regions fall broadly into the class of frontotemporal dementias, and encompass behavioral, dysexecutive, expressive language, and semantic access symptom cores. In brain the characteristic ubiquitin/TDP-43 inclusions are neuronal intranuclear and rarely cytoplasmic or extracellular. The medial temporal lobe, particularly the dentate nucleus, is largely spared. Tau and amyloid pathology are not found. Imaging reveals commensurate frontotemporal atrophy, sometimes lateralized in correlation with the clinical syndrome, accompanied by hypometabolism and hypoperfusion in these anterior regions.

In contrast, cortical regions most affected by FAD PSEN1-associated pathology are connected across the posterior 40% of the corpus callosum and posterior hippocampal commissure – the parietal, superior and inferior temporal lobes and medial temporal lobes but generally sparing the primary occipital region. Neuropathology is described as quite dense and parallels that found in LOAD, e.g., include extracellular neuritic plaques, cytoplasmic fibrillary tangles, neuropil threads and amyloid angiopathy. The temporal lobe, particularly the medial portion is heavily affected. Ubiquitin and TDP-43 are absent. In many cases a classic AD clinical sequence of early memory loss followed by declines in other cognitive domains is described, particularly well documented in PSEN1 E280A families. Variants include EOAD with spastic paraparesis, characteristic "cotton wool" extracellular amyloid plaques and dense amyloid angiopathy. Involvement of the lower motor neuron has not been reported. Structural imaging reveals atrophic changes in temporal and parietal lobes, with hypometabolism, particularly in posterior cingulate and other parietal areas.

Both VCP disease and FAD PSEN1 are single-gene disorders producing dementia phenotypes similar to those seen much more frequently in sporadic disease. In both there is marked variation in phenotypic expression of the same mutation within and across families, and across mutations in the same gene, with overlapping presentations of the FTD or AD dementia phenotypes between genes in some cases. Both VCP and PSEN1 genes have dual roles in both CNS development and in maintenance of the mature nervous system, but produce neurologic dysfunction only in the adult associated with characteristic protein

accumulations. Finally both VCP and PSEN1 pathophysiologic alterations appear to overlap at several points within cellular protein processing and functional pathways, including protein trafficking in the trans-golgi apparatus, downstream in the ubiquitin-proteosome system, and autophagy (Table 4).

IBMPFD Disease: VCP Gene	Familial Alzheimer's Disease: PSEN1 Gene
• Autosomal dominant IBMPFD (OMIM 167320)	• Autosomal dominant FAD (OMIM 104300)
• Single-gene disorder produing dementia phenotype	• Single-gene disorder produing dementia phenotype
• Marked variation of phenotypic expression of the same mutation within and across families	• Marked variation of phenotypic expression of the same mutation within and across families
• Mutation in the valosin-containing protein (VCP) gene	• Mutation in the Presenillin1 (PSEN1) gene, an important component of gamma-secretase that cleaves amyloid precursor protein (APP) & NOTCH
• Currently over 20 known VCP mutations	• Currently over 194 known PSEN1 mutations
• Onset in the 50's	• Onset in the late 40's
• Characterized by abulia, expressive language loss, and executive dysfunction	• Characterized by early memory loss and diffuse amyloid vasculopathy
• Anterior, frontal and temporal lobes pattern of degeneration	• Amyloid plaque and neurofibrillary tau pathology in temporal and parietal lobes, but not ubiquitin or TDP-43
• Neuronal nuclear inclusions of ubiquitin and TDP-43, but not amyloid or tau	• PSEN1 has been implicated in adult neuronal stem cell differentiation, cortical development, ER calcium regulation, and autophagy
• Long tract findings are not described	• Cortical regions affected by FAD PSEN1 pathology are conncected across the posterior 40% of the corpus callosum and posterior hippocampal commissure
• VCP plays a role in ubiquitin-mediated protein degradation, cell cycle control, membrane fusion, and gogi reassembly	• Neuropathology includes extracellular neuritic plaques, cytoplasmic fibrillary tangles, neuropil threads and amyloid angiopathy
• VCP has been implicated in ubiquitin-proteasomal system, ER dysfunction, cell death and autophagy/lysosomal pathways	• Structural imaging reveals atrophic changes in temporal and parietal lobes
• Cortical regions affected by VCP pathology are connected by the anterior 60% of the corpus callosum and anterior commissure	
• Imaging reveals commensurate frontotemporal atrophy accompanied by hypometabolism and hypoperfusion in anterior regions	

Table 4. Neuropathologic Features and Points of Comparison: IBMPFD vs. FAD.

5. Conclusion

VCP disease and FAD PSEN1 appear to have commonalities at a fundamental level in that both involve altered polyfunctional proteins involved in specific overlapping functions, particularly autophagy, and have common downstream pathways, e.g., proteosomal. Yet the diseases are clearly distinct in most particulars, suggesting a principle of independent compartmentalization that may provide insights into both disorders.

6. References

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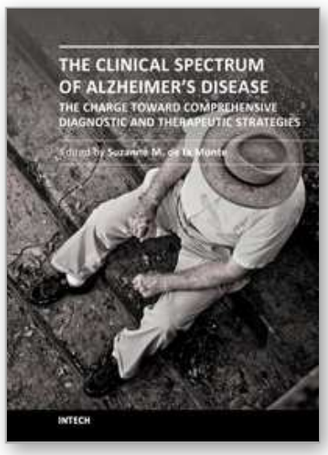

The Clinical Spectrum of Alzheimer's Disease -The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies

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The Clinical Spectrum of Alzheimer's Disease: The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies is highly informative and current. Acknowledged experts in the field critically review both standard and under-appreciated clinical, behavioral, epidemiological, genetic, and neuroimaging attributes of Alzheimer's disease. The collection covers diverse topics of interest to clinicians and researchers alike. Experienced professionals and newcomers to the field will benefit from the read. The strengths and weaknesses of current clinical, non-invasive, neuro-imaging, and biomarker diagnostic approaches are explained. The perspectives give fresh insights into the process of neurodegeneration. Readers will be enlightened by the evidence that the neural circuits damaged by neurodegeneration are much broader than conventionally taught, suggesting that Alzheimer's could be detected at earlier stages of disease by utilizing multi-pronged diagnostic approaches. This book inspires renewed hope that more effective treatments could be developed based upon the expanding list of potential therapeutic targets.

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