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Inclusion Body Myopathy with Paget Disease of Bone and/or Frontotemporal Dementia

[*Inclusion Body Myopathy with Early-Onset Paget Disease of Bone and/or Frontotemporal Dementia, IBMPFD*]

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Summary

Disease characteristics. Inclusion body myopathy associated with Paget disease of bone (PDB) and/or frontotemporal dementia (IBMPFD) is characterized by adult-onset proximal and distal muscle weakness (clinically resembling a limb-girdle muscular dystrophy syndrome), early-onset PDB, and premature frontotemporal dementia (FTD). Muscle weakness progresses to involve other limb and respiratory muscles. Cardiac failure and cardiomyopathy have been observed in later stages. PDB involves focal areas of increased bone turnover that typically lead to spine and/or hip pain and localized enlargement and deformity of the long bones; pathologic fractures occur on occasion. Early stages of FTD are characterized by dysnomia, dyscalculia, comprehension deficits, paraphasic errors, and relative preservation of memory, and later stages by inability to speak, auditory comprehension deficits for even one-step commands, alexia, and agraphia. Mean age at diagnosis for muscle disease and PDB is 42 years; for FTD, 55 years.

Diagnosis/testing. In IBMPFD, the diagnosis of muscle disease is based on serum CK concentration, electromyogram (EMG), and skeletal muscle histology; the diagnosis of PDB on serum alkaline phosphatase (ALP) concentration, urine concentrations of pyridinoline (PYD) and deoxypyridinoline (DPD), and skeletal radiographs or radionuclide scan; and the diagnosis of FTD on comprehensive neuropsychological assessment. *VCP* is the only gene known to be associated with IBMPFD. Sequence analysis in research laboratories identifies mutations in 100% of families who meet diagnostic criteria for IBMPFD and show linkage to 9p21.1-p12. Sequence analysis is available clinically.

Management. *Treatment of manifestations:* weight control to avoid obesity; physical therapy and stretching exercises to promote mobility and prevent contractures; mechanical aids (canes, walkers, orthotics, wheelchairs) for ambulation/mobility; surgical intervention for foot deformity and scoliosis; respiratory aids when indicated; social and emotional support; assisted living arrangements for muscle weakness and/or dementia; bisphosphonates to relieve pain and disability from PDB. *Surveillance:* at periodic intervals: echocardiogram and EKG to monitor for evidence of cardiomyopathy; pulmonary function studies; alkaline phosphatase,

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skeletal x-rays and bone scans to monitor for PDB onset and effectiveness of therapy; assessment of behavior and mental status.

Genetic counseling. IBMPFD is inherited in an autosomal dominant manner. An estimated 80% of affected individuals have an affected parent and approximately 20% have a *de novo* mutation. Each child of an individual with IBMPFD has a 50% chance of inheriting the mutation. No laboratories offering molecular genetic testing for prenatal diagnosis for IBMPFD are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available in a laboratory offering custom prenatal testing for families in which the disease-causing mutation has been identified.

Diagnosis

Clinical Diagnosis

The diagnosis of inclusion body or nonspecific myopathy associated with Paget disease of bone with or without frontotemporal dementia (IBMPFD) is established by the combination of the following:

Myopathy that is usually proximal, progressive, and adult-onset:

- Serum CK concentration is normal to mildly elevated (mean: 195 U/L; range: 40-1145 U/L; normal range: 20-222 U/L).
- EMG (electromyogram) shows myopathic changes, and occasionally neuropathic changes.
- Skeletal muscle pathology is typically nonspecific.
  - Light microscopy of muscle biopsy reveals nonspecific changes: variability in fiber size, type I fiber predominance, and atrophic and hypertrophic fibers. Fibers may contain single or multiple vacuoles. Rimmed vacuoles and cytoplasmic VCP (valosin-containing protein) and ubiquitin-positive inclusions visible in some fibers are characteristic of inclusion body myopathy. The inclusions appear with time and can be observed at a later stage of the disease in some individuals. In advanced cases, severe degenerative muscle changes and fatty replacement of muscle fibers may be noted. Inflammatory cells are absent.
  - Electron microscopy may show nonspecific cytoplasmic changes. The characteristic inclusions composed of randomly oriented tubulofilaments, roughly 15-21 nm in diameter, are seen in muscle nuclei and in cytoplasm. In one family, atrophic and vacuolated muscle fibers containing abundant cytoplasmic-paired helical filaments with epitopes of phosphorylated tau, congophilia, abnormal accumulation ofβ-amyloid precursor protein (βAPP) epitopes, and accumulation of apolipoprotein E (ApoE) were observed [Alvarez et al 1998].

Paget disease of bone (PDB), suspected in individuals with spine or hip pain, bony tenderness, reduced height, pathologic fractures, long-bone or cranial-bone deformity, or hearing loss resulting from eighth-nerve compression by calvarial bony overgrowth. The diagnosis of PDB can be established with the following findings:

- Elevated serum alkaline phosphatase (ALP) concentration (mean: 359 U/L; range: 58-1724 U/L; normal range: 30-130 U/L)
- Elevated urine concentrations of pyridinoline (PYD) and deoxypyridinoline (DPD):

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- Mean PYD: 153 IU/L (normal: 31.1 IU/L)
- Mean DPD: 40 IU/L (normal: 6.8 IU/L)

  Note: The DPD/PYD ratio is not significantly different between affected persons (0.291) and normal controls (0.214).

- Bone findings:
  - Skeletal radiographs reveal diagnostic changes of coarse trabeculation; cortical thickening; and spotty sclerosis in the skull, pelvis, spine, and scapula that later becomes widespread. Radiographic findings of PDB are typically present ten to 15 years before the diagnosis of PDB can be made based on clinical findings.

    OR

  - Radionuclide scan shows focally increased bony uptake (a more sensitive indicator of PDB than skeletal radiographs).

Frontotemporal dementia (FTD), diagnosed by comprehensive neuropsychological assessment that reveals behavioral alteration (e.g., personal/social unawareness, perseveration, disinhibition), early expressive or receptive language dysfunction, and relative preservation of memory, orientation, and praxis [Miller et al 1997]:

- Imaging studies reveal atrophy of anterior temporal and frontal lobes.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. *VCP*, encoding valosin-containing protein (VCP), a member of the AAA-ATPase superfamily, is the only gene known to be associated with inclusion body myopathy with Paget disease and frontotemporal dementia (IBMPFD).

Note:

- In all families with IBMPFD that link to 9p, *VCP* mutations have been identified.
- In families with isolated PDB that link to 9p, *VCP* mutations have not been identified [Lucas et al 2006].

Other loci. Several families who meet diagnostic criteria for IBMPFD have not had *VCP* mutations or shown linkage to 9p21.2 [Authors, unpublished data], suggesting genetic heterogeneity for this disorder.

Clinical testing

- **Sequence analysis.** A *VCP* mutation has been identified in all families with IBMPFD that link to 9p (see Table 2 for specific mutations identified) [Author, personal observation].

Research testing

- **Targeted mutation analysis.** Using a panel of the ten known mutations*, mutations would be identified in 27/37 (70%) of probands [Author, personal observation].

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* p.Arg93Cys, p.Arg95Gly, p.Arg191Gln, p.Arg155Cys, p.Arg155Cys, p.Arg155Pro, p.Arg159His, p.ALa232Glu, p.Leu198Trp, p.Asn387His

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Inclusion Body Myopathy with Paget Disease of Bone and/or Frontotemporal Dementia

Test Method	Mutations Detected	Mutation Detection Frequency by Test Method	Test Availability
Sequence analysis	*VCP* sequence variants	100% [1]	Clinical Testing

1. In families who meet diagnostic criteria for IBMPFD and show linkage to 9p21.1-p12

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *VCP*.

Clinical Description

Natural History

Inclusion body myopathy associated with Paget disease of bone (PDB) and/or frontotemporal dementia (IBMPFD) is characterized by adult-onset proximal and distal muscle weakness (clinically resembling a limb-girdle muscular dystrophy syndrome), early-onset PDB in most cases, and premature frontotemporal dementia (FTD).

The association of inclusion body myopathy and frontotemporal dementia was established by Kovach et al (2001) among 49 affected individuals from the original family described by Kimonis et al (2000) and three other unrelated families.

The phenotype has been expanded based on findings in affected individuals from 27 families from North and South America and Europe harboring *VCP* missense mutations [Haubenberger et al 2005; Schroder et al 2005; Guyant-Marechal et al 2006; Hübbers et al 2007; Kimonis et al, in press].

Kimonis et al (in press) reviewed the clinical variability in 29 individuals among nine families, in whom the diagnosis was confirmed by the presence of a *VCP* mutation. In those individuals, diagnoses that had been considered before the diagnosis of IBMPFD was established by molecular genetic testing included the following: limb-girdle muscular dystrophy (LGMD) (11 persons); scapuloperoneal muscular dystrophy (SPMD) (8); amyotrophic lateral sclerosis (ALS) (3); spinal muscular atrophy (SMA) (2); diabetic neuropathy (2); inclusion body myositis (1); multiple sclerosis (1); polymyositis (1); facioscapulohumeral (FSH) muscular dystrophy (1); and distal myopathy/ oculopharyngeal muscular dystrophy/ myofibrillar myopathy (1). The remaining individuals were diagnosed with a nonspecific myopathy. Several persons had more than one diagnosis made over the course of their illness.

Myopathy. In families studied thus far, 92% of affected individuals had proximal limb-girdle weakness. Diagnosis was at a mean age of 42 years (range: 3-61 years; typically 20s-40s). Muscle weakness is usually proximal, involving the hip and shoulder girdle muscles; however, several individuals have had initial weakness of the distal muscles of the hands and feet. Affected individuals experience difficulty walking upstairs and raising the arms above the shoulders. The gait is typically waddling and the stance lordotic.

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Weakness progresses and other limb and respiratory muscle groups become involved over time. Many affected individuals become unable to walk and are wheelchair bound.

Death typically occurs in the 50s-60s from progressive respiratory and cardiac failure.

Dilated cardiomyopathy. In several individuals in the first family originally reported by Kimonis et al (2000) with limb-girdle myopathy and Paget disease of bone, cardiac failure and cardiomyopathy were noted in the later stages of the disease. Hübbers et al (2007) reported dilated cardiomyopathy in a woman with the common mutation characterized by ubiquitin-positive cytoplasmic aggregates and nuclear inclusions. See Dilated Cardiomyopathy Overview.

Paget disease of bone (PDB). In families studied thus far, 51% of affected individuals had PDB. Mean age at diagnosis was 42 years (range: 31-61 years). PDB was occasionally asymptomatic, but was diagnosed based on the serum concentration of alkaline phosphatase; therefore, it may be underdiagnosed.

PDB involves focal areas of increased bone turnover that lead to complications such as bone pain, localized painful enlargement and deformity of the long bones, pathologic fractures (rare), and deafness. PDB typically manifests as spine and/or hip pain.

Frontotemporal dementia. FTD is a degenerative condition of the frontal and anterior temporal lobes that differs from the dementia seen in disorders such as Alzheimer disease (see Alzheimer Disease Overview), Pick disease, and Creutzfeldt-Jakob disease (see Prion Diseases). The areas of the brain affected by FTD control reasoning, personality, movement, speech, social graces, and language; memory is preserved.

Among those studied, features were consistent with frontotemporal dementia. In the early stages, dysnomia, dyscalculia, comprehension deficits, and paraphasic errors were evident. Adjusting for aphasia, episodic memory is minimally impaired in the early stages. Progressive aphasia with inability to speak, auditory comprehension deficits for even one-step commands, alexia, and agraphia are noted.

In families studied thus far, approximately 30% of affected individuals had frontotemporal dementia. Mean age at diagnosis of dementia was 55 years (range: 42-61 years). Several individuals were in advanced stages of dementia when diagnosed with IBMPFD.

Other phenotypes associated with mutations in *VCP* include isolated:

- Proximal limb-girdle myopathy
- Paget disease of bone
- Dementia

[Kimonis et al 2000; Kovach et al 2001; Haubenberger et al 2005; Schroder et al 2005; Guyant-Marechal et al 2006; Hübbers et al 2007; Kimonis et al, in press]

Neuropathology. A systematic analysis of the neuropathologic changes in eight persons with IBMPFD and *VCP* mutations revealed a novel pattern of ubiquitin pathology, characterized by ubiquitin-positive neuronal intranuclear inclusions, dystrophic neuritis, and rare intracytoplasmic inclusions. The ubiquitin pathology was abundant in the neocortex, less robust in limbic and subcortical nuclei, and absent in the dentate gyrus. Only rare inclusions were detected with antibodies to VCP and TDP-43 [Forman et al 2006, Neumann et al 2007]. These findings support the hypothesis that neuropathologic changes associated with *VCP* gene mutations result from impairment of ubiquitin-based degradation pathways.

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Genotype-Phenotype Correlations

Clinical, radiologic, biochemical, and mutation data were analyzed in 103 individuals from 14 families:

- Individuals with the p.Arg155Cys mutation had an earlier age of onset of IBM ($p=0.01$) and those with the p.Arg155His mutation had a later onset of PDB ($p<0.05$) compared to the others [Watts et al, in preparation].
- A mutation in the main catalytic D1 ATPase domain of *VCP* (p.Ala232Glu) essential for hexamer formation was found in a single family with a more aggressive type of disease.

Because of the range of phenotypes associated with mutations in *VCP*, several studies have looked at modifier genes:

- From a database of 231 members of 15 families, 174 had APOE genotype available for regression analysis. Analysis of the data suggests a potential link between APOE e4 genotype and the frontotemporal dementia found in IBMPFD [Mehta et al 2007].
- No association was observed between frontotemporal dementia and microtubule associated protein tau (MAPT) H2 haplotype ($p=0.5$) [Author, personal observation].

Penetrance

Penetrance is almost complete; however, it is age related.

Penetrance by phenotype (Figure 1)

- Presence of all three major manifestations: 12% of affected individuals
- Presence of only two major manifestations in any combination: 50% of affected individuals
- Each of the three major manifestations as an apparently isolated finding:
  - Myopathy (IBM): 30%
  - Paget disease of bone (PDB): 5%
  - Frontotemporal dementia (FTD): 3%

Anticipation

There is no evidence of anticipation in IBMPFD.

Prevalence

IBMPFD is rare; the true prevalence is unknown. Twenty-six families have been studied by the authors, who believe the disorder to be underdiagnosed.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

The differential diagnosis of inclusion body myopathy with Paget disease and frontotemporal dementia (IBMPFD) includes the following disorders:

Limb-girdle muscular dystrophy (LGMD). Because the muscle biopsy is nonspecific in the majority of individuals with IBMPFD, the disorder has been labeled as an LGMD.

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Inclusion body myopathy type 2 (IBM2). IBM2 is characterized by adult-onset, slowly progressive distal muscle weakness that begins with gait disturbance and foot drop secondary to anterior tibialis muscle weakness. Weakness eventually includes the hand and thigh muscles, but commonly spares the quadriceps muscles, even in advanced disease. Affected individuals are usually wheelchair bound approximately 20 years after onset. If quadriceps sparing is incomplete, loss of ambulation tends to occur earlier. Muscle histopathology typically shows rimmed vacuoles and characteristic filamentous inclusions. The gene *GNE*, which encodes the bifunctional enzyme UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase, is the only gene associated with IBM2. Inheritance is autosomal recessive [Eisenberg et al 2001].

Sporadic inclusion-body myositis (sIBM) is the most common acquired muscle disease in Caucasians over age 50 years. Pathologically it is characterized by inflammatory, degenerative, and mitochondrial changes that interact in an as-yet-unknown manner to cause progressive muscle degeneration and weakness. The cause is unknown, but it is thought to involve a complex interplay between environmental factors, genetic susceptibility, and aging [Askanas & Engel 2002].

Facioscapulohumeral muscular dystrophy (FSHD) FSHD typically presents before age 20 years with weakness of the facial muscles and the stabilizers of the scapula or the dorsiflexors of the foot. Severity is variable. Weakness is slowly progressive and approximately 20% of affected individuals eventually require a wheelchair. Life expectancy is not shortened. Inheritance is autosomal dominant.

Scapuloperoneal myopathy (SPM) (also known as scapuloperoneal muscular dystrophy (SPMD) or scapuloperoneal syndrome, myopathic type). Scapuloperoneal syndromes are heterogeneous. They are characterized by weakness in the distribution of the shoulder girdle and peroneal muscles. Scapuloperoneal myopathy can resemble FSHD clinically. The locus for SPMD has been assigned to 12q [Wilhelmsen et al 1996].

Amyotrophic lateral sclerosis (ALS). Because of asymmetric involvement and association of both distal and proximal muscle groups, individuals with IBMPFD have been misdiagnosed as ALS.

Paget disease of bone (PDB). Genetic heterogeneity is found [Cody et al 1997, Hocking et al 2002, Laurin et al 2002]. Germline mutations of the gene encoding sequestosome 1 have been implicated in Paget disease of bone. A mutation hot spot (p.Pro392Leu) was identified in the ubiquitin-associated domain (UBA) that accounts for 16% of simplex cases (i.e., a single occurrence in a family) and 46% of familial cases in the French Canadian population.

Frontotemporal dementia (FTD) causes a substantial proportion of primary degenerative dementia occurring before age 65 years [Chow et al 1999].

Frontotemporal dementia with parkinsonism-17 (FTDP-17) is a presenile dementia affecting the frontal and temporal cortex and some subcortical nuclei. Clinical presentation is variable. Individuals may present with slowly progressive behavioral changes, language disturbances, and/or extrapyramidal signs. Some present with rigidity, bradykinesia, supranuclear palsy, and saccadic eye movement disorders. Symptoms usually start between ages 40 and 60 years, but may occur earlier or later. Disease duration is usually between five and ten years, but occasionally may be up to 20 to 30 years. The disease progresses over a few years into a profound dementia with mutism. MAPT encoding microtubule-associated protein tau is the only gene known to be associated with FTDP-17. Inheritance is autosomal dominant [Hutton et al 1998].

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Alzheimer disease. Imaging studies in IBMPFD reveal atrophy of anterior temporal and frontal lobes. By contrast, more widespread atrophy or perfusion deficits, for example involving parietal lobes, are more compatible with Alzheimer disease.

Other disorders. An autosomal dominant disorder associated with progressive myopathy of a limb-girdle distribution, bone fragility, poor healing of long bones, premature graying with thin hair, thin skin, hernias, and clotting disorders that may resemble IBMPFD has been described in a single family [Mehta et al 2006]. Skeletal radiographs demonstrate coarse trabeculation, patchy sclerosis, cortical thickening, and narrowing of medullary cavities. A genome-wide scan mapped the disorder to chromosome 9p21-p22, the region in which diaphyseal medullary stenosis with malignant fibrous histiocytoma (DMS-MFH) also maps, suggesting possible allelic heterogeneity [Watts et al 2005].

Waggoner et al (2002) reported a ten-member family with autosomal dominant PDB and a scapuloperoneal type of muscular dystrophy. Molecular analyses excluded all known loci for Paget disease of bone, scapuloperoneal muscular dystrophy (SPMD), facioscapulohumeral muscular dystrophy (FSHD), amyotrophic lateral sclerosis (ALS), Bethlem myopathy, two forms of autosomal dominant limb-girdle muscular dystrophy (LGMD), and the critical region for LGMD or HIBM/PDB on chromosome 9p21.1-q12. A genome-wide search identified linkage to chromosome 16q 22.3-q24.1 [Watts et al, in preparation], a locus known to contain a quantitative trait locus (QTL) [Ralston et al 2005].

Nasu Hakola disease (also known as PLOSL) is a presenile dementia associated with loss of myelin, basal ganglia calcification, and bone cysts. It is caused by recessively inherited mutations in the two genes *TREM2* and *DAP12*, which encode subunits of a cell membrane-associated receptor complex [Paloneva et al 2002].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with inclusion body myopathy with Paget disease and frontotemporal dementia (IBMPFD), the following evaluations are recommended:

- Assessment of muscle strength, muscle wasting and tendon reflexes. EMG and/or muscle biopsy may be necessary.
- Baseline pulmonary function studies
- Cardiac evaluation by echocardiogram and ECG
- Blood alkaline phosphatase, urine pyridinoline studies and, if indicated, skeletal x-ray or bone scan studies to evaluate distribution and severity of Paget disease of the bone
- Baseline neuropsychological studies of behavior and mental status

Treatment of Manifestations

Myopathy. Management should be tailored to each individual. A general approach to appropriate management can prolong survival and improve quality of life. This general approach is based on the typical progression and complications of individuals with LGMD as described by McDonald et al (1995) and Bushby (1999).

- Weight control to avoid obesity

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- Physical therapy and stretching exercises to promote mobility and prevent contractures
- Use of mechanical aids such as canes, walkers, orthotics, and wheelchairs as needed to help ambulation and mobility
- Surgical intervention as needed for orthopedic complications such as foot deformity and scoliosis
- Use of respiratory aids when indicated
- Social and emotional support and stimulation to maximize a sense of social involvement and productivity and to reduce the sense of social isolation common in these disorders [Eggers & Zatz 1998]
- Assisted living arrangements as necessitated by muscle weakness and/or dementia

Paget disease of bone. Treatment with the following potent bisphosphonates can reduce the alkaline phosphatase concentration and relieve pain and disability:

- Actonel®/risedronate
- Fosamax®/alendronate
- Aredia®/pamidronate

Surveillance

At periodic intervals:

- Echocardiogram and EKG to monitor for evidence of cardiomyopathy
- Pulmonary function studies
- Alkaline phosphatase, skeletal x-rays, and bone scans for monitoring of the PDB if symptomatic and for monitoring of therapy
- Monitoring of behavior and mental status

Testing of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

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Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Inclusion body myopathy with Paget disease and frontotemporal dementia (IBMPFD) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Approximately 80% of individuals diagnosed with IBMPFD have an affected parent.
- A proband with IBMPFD may have the disorder as the result of a new gene mutation. The proportion of cases caused by *de novo* mutations is an estimated 20% or greater.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include clinical evaluation by a neurologist familiar with myopathic disorders in addition to laboratory evaluation of CPK and alkaline phosphatase concentrations.

Note: Although approximately 80% of individuals diagnosed with IBMPFD have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.

Offspring of a proband. Each child of an individual with IBMPFD has a 50% chance of inheriting the mutation.

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

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Family planning. The optimal time for determination of genetic risk is before pregnancy. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis for IBMPFD are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutation has been identified. For laboratories offering custom prenatal testing, see Testing.

Requests for prenatal testing for adult-onset conditions such as IBMPFD are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Inclusion Body Myopathy with Paget Disease of Bone and/or Frontotemporal Dementia

Gene Symbol	Chromosomal Locus	Protein Name
VCP	9p13-p12	Transitional endoplasmic reticulum ATPase

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Inclusion Body Myopathy with Paget Disease of Bone and/or Frontotemporal Dementia

167320	INCLUSION BODY MYOPATHY WITH EARLY-ONSET PAGET DISEASE AND FRONTOTEMPORAL DEMENTIA; IBMPFD
601023	VALOSIN-CONTAINING PROTEIN; VCP

Table C. Genomic Databases for Inclusion Body Myopathy with Paget Disease of Bone and/or Frontotemporal Dementia

Gene Symbol	Entrez Gene	HGMD
VCP	7415 (MIM No. 601023)	VCP

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants: *VCP* has 17 exons.

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Pathologic allelic variants: Mutations in the 27 families studied to date are summarized in Table 2. Mutations in all but one family cluster in the N-terminal CDC48 domain involved in ubiquitin binding.

Table 2. Mutations in VCP Identified in 27 Families

Amino Acid	Base Change (ORF)	Exon	Exon bp	Number of Families
p.Arg93Cys	277C>T	3	148	4
p.Arg95Gly	283C>G	3	154	2
p.Arg155Cys	463C>T	5	18	5
p.Arg155His	464G>A	5	19	8
p.Arg155Pro	464G>C	5	19	1
p.Arg159His	476G>A	5	31	1
p.Arg191Gln	572G>A	5	127	3
p.Leu198Trp	593T>G	6	17	1
p.Ala232Glu	695C>A	6	119	1
p.Asn387His	1159A>C	10	78	1

Watts et al 2004; Haubenberger et al 2005; Schroder et al 2005; Guyant-Marechal et al 2006; Hübbers et al 2007; Watts et al, in preparation

Normal gene product: The 97-kd valosin-containing protein is a member of the type II AAA ATPases (ATPases associated with a variety of activities), characterized by the presence of two conserved ATPase domains, also called AAA domains. Similar to other AAA proteins, VCP is an enzymatic machine. It catalyzes ATP hydrolysis to generate energy and uses the energy to perform mechanical work in cells. VCP is involved in an unusually wide variety of functions and is associated with distinct and crucial cell protein pathways, namely cell cycle control homotypic membrane fusion, nuclear envelope reconstruction, postmitotic organelle reassembly, and ubiquitin-dependent protein degradation [Rabouille et al 1998, Hetzer et al 2001, Rabinovich et al 2002]. VCP forms a homohexamer and binds to several different adapter proteins, enabling VCP to target specific substrates for degradation [Kondo et al 1997, Meyer et al 2000]. VCP plays a critical role in the endoplasmic reticulum (ER)-associated degradation (ERAD) pathway during the "quality control process" that selectively eliminates aberrant proteins in the secretory pathway [Jarosch et al 2002]. This pathway also targets destruction of protein substrates dislocated from the ER to the cytosol, where ubiquitination and degradation occur by the 26S proteasome [Dai & Li 2001].

Abnormal gene product: *VCP* mutations in families with IBMPFD cluster in the N-terminal CDC48 domain, involved in ubiquitin binding [Dai & Li 2001, Rape et al 2001]. This highly structured domain forms two distinct regions — the double ψ barrel (amino acids 25-106) and the four-stranded β barrel (amino acids 112-186) — connected by a short linker region (amino acids 107-111). VCP forms a homohexamer in which the D1/D2 domains bind in a head-to-tail ring [Zhang et al 2000], allowing the N-terminal domain to undergo conformational changes without affecting the stability of the homohexamer ring structure.

VCP missense mutations causing IBMPFD disrupt either the double ψ barrel (p.Arg93Cys, p.Arg95Gly/Cys), or the four-stranded β barrel (p.Arg155Cys/His/Pro, p.Arg159His), or the flexible linker (p.Arg191Gln; family 13). Hence, the affected ubiquitin-binding domain may possibly impair N-terminal domain binding of specific partner proteins. Most of the mutated residues are adjacent and potentially interact with each other (p.Arg155-p.Asn387, p.Arg159-p.Ala232 and p.Arg191-p.Leu198), suggesting that these residues may have a similar and specific function within the VCP homohexamer.

Growing evidence implicates VCP in neuronal degeneration. Several in vitro studies, using neuronally differentiated mammalian cell lines, show that mutations in the D2 domain of *VCP* are associated with polyubiquitinated proteins that accumulate in nuclear and membrane cellular fractions and induce cytoplasmic vacuoles. VCP also binds to expanded polyglutamine (poly-Q) protein aggregates. The poly-Q binding domain of human VCP maps to amino acid residues 142-200, encompassing a region of the N domain and linker (N domain to D1) domain.

Animal models for IBMPFD

Resources

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The Paget Foundation
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Email: Pagetfdn@aol.com
www.paget.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Alvarez A, Simmons Z, Engel WK, Askanas V. New autosomal dominant inclusion body myopathy (AD-IBM) with many congophilic muscle nuclei that contain paired-helical filaments (PHFs) composed of phosphorylated tau. Neuro. 1998;50:A204.

Askanas V, Engel WK. Inclusion-body myositis and myopathies: different etiologies, possibly similar pathogenic mechanisms. Curr Opin Neurol. 2002;15:525–31. [PubMed: 12351995]

Bushby KM. The limb-girdle muscular dystrophies-multiple genes, multiple mechanisms. Hum Mol Genet. 1999;8:1875–82. [PubMed: 10469840]

Chow TW, Miller BL, Hayashi VN, Geschwind DH. Inheritance of frontotemporal dementia. Arch Neurol. 1999;56:817–22. [PubMed: 10404983]

Cody JD, Singer FR, Roodman GD, Otterund B, Lewis TB, Leppert M, Leach RJ. Genetic linkage of Paget disease of the bone to chromosome 18q. Am J Hum Genet. 1997;61:1117–22. [PubMed: 9345096]

Dai RM, Li CC. Valosin-containing protein is a multi-ubiquitin chain-targeting factor required in ubiquitin-proteasome degradation. Nat Cell Biol. 2001;3:740–4. [PubMed: 11483959]

Eggers S, Zatz M. Social adjustment in adult males affected with progressive muscular dystrophy. Am J Med Genet. 1998;81:4–12. [PubMed: 9514580]

Eisenberg I, Avidan N, Potikha T, Hochner H, Chen M, Olender T, Barash M, Shemesh M, Sadeh M, Grabov-Nardini G, Shmilevich I, Friedmann A, Karpati G, Bradley WG, Baumbach L, Lancet D, Asher EB, Beckmann JS, Argov Z, Mitrani-Rosenbaum S. The UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase gene is mutated in recessive hereditary inclusion body myopathy. Nat Genet. 2001;29:83–7. [PubMed: 11528398]

Forman MS, Mackenzie IR, Cairns NJ, Swanson E, Boyer PJ, Drachman DA, Jhaveri BS, Karlawish JH, Pestronk A, Smith TW, Tu PH, Watts GD, Markesbery WR, Smith CD, Kimonis VE. Novel ubiquitin neuropathology in frontotemporal dementia with valosin-containing protein gene mutations. J Neuropathol Exp Neurol. 2006;65:571–81. [PubMed: 16783167]

Guyant-Marechal L, Laquerriere A, Duyckaerts C, Dumanchin C, Bou J, Dugny F, Le Ber I, Frebourg T, Hannequin D, Campion D. Valosin-containing protein gene mutations: clinical and neuropathologic features. Neurology. 2006;67:644–51. [PubMed: 16790606]

Haubenberger D, Bittner RE, Rauch-Shorny S, Zimprich F, Mannhalter C, Wagner L, Mineva I, Vass K, Auff E, Zimprich A. Inclusion body myopathy and Paget disease is linked to a novel mutation in the VCP gene. Neurology. 2005;65:1304–5. [PubMed: 16247064]

Hetzer M, Meyer HH, Walther TC, Bilbao-Cortes D, Warren G, Mattaj IW. Distinct AAA-ATPase p97 complexes function in discrete steps of nuclear assembly. Nat Cell Biol. 2001;3:1086–91. [PubMed: 11781570]

Hocking LJ, Lucas GJ, Daroszewska A, Mangion J, Olavesen M, Cundy T, Nicholson GC, Ward L, Bennett ST, Wuyts W, Van Hul W, Ralston SH. Domain-specific mutations in sequestosome 1

GeneReviews GeneReviews GeneReviews GeneReviews

GeneReviews GeneReviews GeneReviews GeneReviews

(SQSTM1) cause familial and sporadic Paget's disease. Hum Mol Genet. 2002;11:2735–9. [PubMed: 12374763]

Hubbers CU, Clemen CS, Kesper K, Boddrich A, Hofmann A, Kamarainen O, Tolksdorf K, Stumpf M, Reichelt J, Roth U, Krause S, Watts G, Kimonis V, Wattjes MP, Reimann J, Thal DR, Biermann K, Evert BO, Lochmuller H, Wanker EE, Schoser BG, Noegel AA, Schroder R. Pathological consequences of VCP mutations on human striated muscle. Brain. 2007;130:381–93. [PubMed: 16984901]

Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, Houlden H, Pickering-Brown S, Chakraverty S, Isaacs A, Grover A, Hackett J, Adamson J, Lincoln S, Dickson D, Davies P, Petersen RC, Stevens M, de Graaff E, Wauters E, van Baren J, Hillebrand M, Joosse M, Kwon JM, Nowotny P, Che LK, Norton J, Morris JC, Reed LA, Trojanowski J, Basun H, Lannfelt L, Neystat M, Fahn S, Dark F, Tannenberg T, Dodd PR, Hayward N, Kwok JB, Schofield PR, Andreadis A, Snowden J, Craufurd D, Neary D, Owen F, Oostra BA, Hardy J, Goate A, van Swieten J, Mann D, Lynch T, Heutink P. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. Nature. 1998;393:702–5. [PubMed: 9641683]

Jarosch E, Geiss-Friedlander R, Meusser B, Walter J, Sommer T. Protein dislocation from the endoplasmic reticulum--pulling out the suspect. Traffic. 2002;3:530–6. [PubMed: 12121416]

Kimonis VE, Kovach MJ, Waggoner B, Leal S, Salam A, Rimer L, Davis K, Khardori R, Gelber D. Clinical and molecular studies in a unique family with autosomal dominant limb-girdle muscular dystrophy and Paget disease of bone. Genet Med. 2000;2:232–41. [PubMed: 11252708]

Kimonis VE, Mehta S, Wymer J, Pasquali M, Kartashov A, Smith CD, Boycott K, Neilan E, Kimonis K, Brownell AKW, Mumm S, M Watts G. Clinical and molecular studies in nine families with familial myopathy, Paget disease of bone and frontotemporal dementia. Am J Med Genet . in press

Kondo H, Rabouille C, Newman R, Levine TP, Pappin D, Freemont P, Warren G. p47 is a cofactor for p97-mediated membrane fusion. Nature. 1997;388:75–8. [PubMed: 9214505]

Kovach MJ, Waggoner B, Leal SM, Gelber D, Khardori R, Levenstien MA, Shanks CA, Gregg G, Al-Lozi MT, Miller T, Rakowicz W, Lopate G, Florence J, Glosser G, Simmons Z, Morris JC, Whyte MP, Pestronk A, Kimonis VE. Clinical delineation and localization to chromosome 9p13.3-p12 of a unique dominant disorder in four families: hereditary inclusion body myopathy, Paget disease of bone, and frontotemporal dementia. Mol Genet Metab. 2001;74:458–75. [PubMed: 11749051]

Laurin N, Brown JP, Morissette J, Raymond V. Recurrent mutation of the gene encoding sequestosome 1 (SQSTM1/p62) in Paget disease of bone. Am J Hum Genet. 2002;70:1582–8. [PubMed: 11992264]

Lucas GJ, Mehta SG, Hocking LJ, Stewart TL, Cundy T, Nicholson GC, Walsh JP, Fraser WD, Watts GD, Ralston SH, Kimonis VE. Evaluation of the role of Valosin-containing protein in the pathogenesis of familial and sporadic Paget's disease of bone. Bone. 2006;38:280–5. [PubMed: 16199218]

McDonald CM, Johnson ER, Abresch RT, Carter GT, Fowler WM Jr, Kilmer DD. Profiles of neuromuscular diseases. Limb-girdle syndromes. Am J Phys Med Rehabil. 1995;74:S117–30. [PubMed: 7576419]

Mehta SG, Watts GD, Adamson JL, Hutton M, Umberger G, Xiong S, Ramdeen S, Lovell MA, Kimonis VE, Smith CD. APOE is a potential modifier gene in an autosomal dominant form of frontotemporal dementia (IBMPFD). Genet Med. 2007;9:9–13. [PubMed: 17224685]

Mehta SG, Watts GD, McGillivray B, Mumm S, Hamilton SJ, Ramdeen S, Novack D, Briggs C, Whyte MP, Kimonis VE. Manifestations in a family with autosomal dominant bone fragility and limb-girdle myopathy. Am J Med Genet A. 2006;140:322–30. [PubMed: 16419137]

Meyer HH, Shorter JG, Seemann J, Pappin D, Warren G. A complex of mammalian ufd1 and npl4 links the AAA-ATPase, p97, to ubiquitin and nuclear transport pathways. EMBO J. 2000;19:2181–92. [PubMed: 10811609]

Miller BL, Ikonte C, Ponton M, Levy M, Boone K, Darby A, Berman N, Mena I, Cummings JL. A study of the Lund-Manchester research criteria for frontotemporal dementia: clinical and single-photon emission CT correlations. Neurology. 1997;48:937–42. [PubMed: 9109881]

Neumann M, Mackenzie IR, Cairns NJ, Boyer PJ, Markesbery WR, Smith CD, Taylor JP, Kretzschmar HA, Kimonis VE, Forman MS. TDP-43 in the ubiquitin pathology of frontotemporal dementia with VCP gene mutations. J Neuropathol Exp Neurol. 2007;66:152–7. [PubMed: 17279000]

GeneReviews GeneReviews GeneReviews GeneReviews

Paloneva J, Manninen T, Christman G, Hovanes K, Mandelin J, Adolfsson R, Bianchin M, Bird T, Miranda R, Salmaggi A, Tranebjaerg L, Konttinen Y, Peltonen L. Mutations in two genes encoding different subunits of a receptor signaling complex result in an identical disease phenotype. Am J Hum Genet. 2002;71:656–62. [PubMed: 12080485]

Rabinovich E, Kerem A, Frohlich KU, Diamant N, Bar-Nun S. AAA-ATPase p97/Cdc48p, a cytosolic chaperone required for endoplasmic reticulum-associated protein degradation. Mol Cell Biol. 2002;22:626–34. [PubMed: 11756557]

Rabouille C, Kondo H, Newman R, Hui N, Freemont P, Warren G. Syntaxin 5 is a common component of the Cell. 1998;92:603–10. [PubMed: 9506515]

Ralston SH, Galwey N, MacKay I, Albagha OM, Cardon L, Compston JE, Cooper C, Duncan E, Keen R, Langdahl B, McLellan A, O'Riordan J, Pols HA, Reid DM, Uitterlinden AG, Wass J, Bennett ST. Loci for regulation of bone mineral density in men and women identified by genome wide linkage scan: the FAMOS study. Hum Mol Genet. 2005;14:943–51. [PubMed: 15746152]

Rape M, Hoppe T, Gorr I, Kalocay M, Richly H, Jentsch S. Mobilization of processed, membrane-tethered SPT23 transcription factor by CDC48(UFD1/NPL4), a ubiquitin-selective chaperone. Cell. 2001;107:667–77. [PubMed: 11733065]

Schroder R, Watts GD, Mehta SG, Evert BO, Broich P, Fliessbach K, Pauls K, Hans VH, Kimonis V, Thal DR. Mutant valosin-containing protein causes a novel type of frontotemporal dementia. Ann Neurol. 2005;57:457–61. [PubMed: 15732117]

Waggoner B, Kovach MJ, Winkelman M, Cai D, Khardori R, Gelber D, Kimonis VE. Heterogeneity in familial dominant Paget disease of bone and muscular dystrophy. Am J Med Genet. 2002;108:187–91. [PubMed: 11891683]

Watts GD, Mehta SG, Zhao C, Ramdeen S, Hamilton SJ, Novack DV, Mumm S, Whyte MP, Mc Gillivray B, Kimonis VE. Mapping autosomal dominant progressive limb-girdle myopathy with bone fragility to chromosome 9p21-p22: a novel locus for a musculoskeletal syndrome. Hum Genet. 2005;118:508–14. [PubMed: 16244874]

Watts GD, Wymer J, Kovach MJ, Mehta SG, Mumm S, Darvish D, Pestronk A, Whyte MP, Kimonis VE. Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. Nat Genet. 2004;36:377–81. [PubMed: 15034582]

Watts GDJ, Ramdeen SK, Fulchiero EC, Mehta SG, Drachman DA, Weihl CC, Jamrozik Z, Kwiecinski H, Kaminska A, Kimonis VE. Novel VCP Mutations in Inclusion Body Myopathy associated with Paget Disease of Bone and Frontotemporal Dementia. in preparation

Wilhelmsen KC, Blake DM, Lynch T, Mabutas J, De Vera M, Neystat M, Bernstein M, Hirano M, Gilliam TC, Murphy PL, Sola MD, Bonilla E, Schotland DL, Hays AP, Rowland LP. Chromosome 12-linked autosomal dominant scapuloperoneal muscular dystrophy. Ann Neurol. 1996;39:507–20. [PubMed: 8619529]

Zhang X, Shaw A, Bates PA, Newman RH, Gowen B, Orlova E, Gorman MA, Kondo H, Dokurno P, Lally J, Leonard G, Meyer H, van Heel M, Freemont PS. Structure of the AAA ATPase p97. Mol Cell. 2000;6:1473–84. [PubMed: 11163219]

Chapter Notes

Author Notes

Web site: www.ucihs.uci.edu/pediatrics/drkimonis/index.shtml

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Revision History

- 5 March 2008 (cd) Revision: sequence analysis available clinically
- 25 May 2007 (me) Review posted to live Web site

- 18 November 2004 (vk, gw) Original submission

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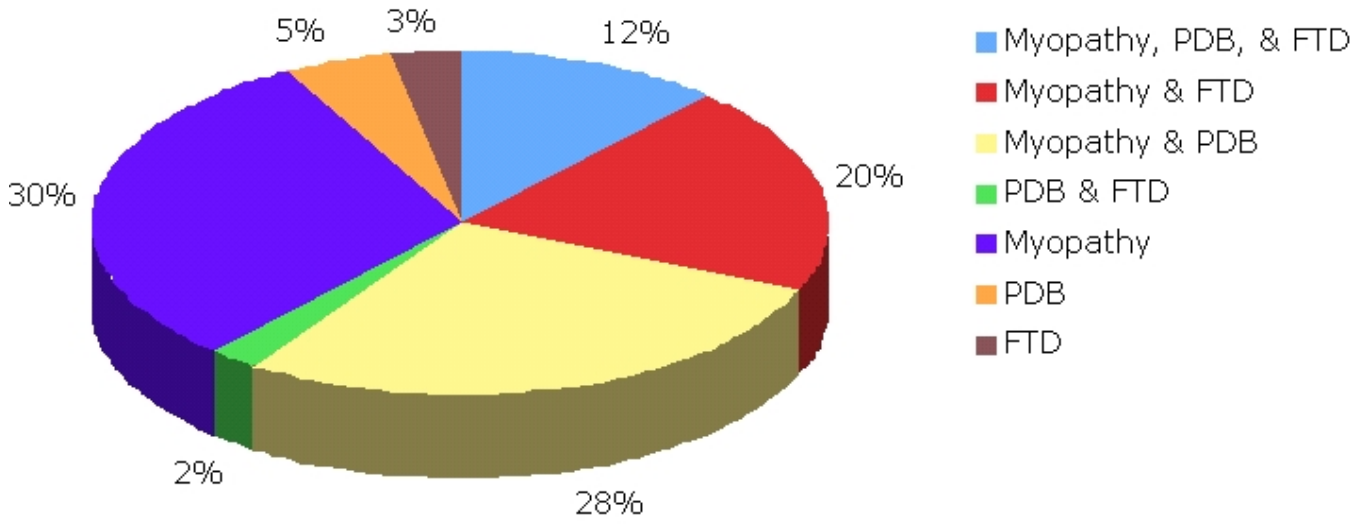

Figure 1. IBMPFD phenotypes

VCP Models

A *Drosophila* VCP (ter94) loss-of-function mutant has been identified as a dominant suppressor of expanded polyglutamine (poly-Q)-induced neuronal degeneration. This suggests that a gene dosage response for VCP expression is crucial to its function in expanded polyglutamine (poly-Q)-induced neuronal degeneration. To further support this, in transgenic *Drosophila*, in which VCP levels were elevated, severe apoptotic cell death was induced, whereas homozygous VCP loss-of-function mutants were embryonically lethal [Hirabayashi et al 2001].

A homozygous knock-out mouse model for VCP was embryonically lethal, the heterozygotes apparently being asymptomatic [Muller et al 2007]. Heterozygous p97+/- mice were indistinguishable from their wild-type littermates, whereas homozygous mutants did not survive to birth and died at a peri-implantation stage. These results show that p97 is an essential gene for early mouse development. Weihl et al (2007) reported their transgenic mice expressing p97/VCP-WT or the most common IBMPFD mutant, p97/VCP Arg155His, under a muscle-specific promoter. The latter became progressively weaker starting at age six months, a finding that coincided with abnormal muscle pathology including coarse internal architecture, vacuolation, and disorganized membrane morphology with reduced caveolin-3 expression at the sarcolemma. There was an increase in ubiquitin-containing protein inclusions and high molecular-weight ubiquitinated proteins, markers of ubiquitin-proteasome system (UPS) dysfunction.

Hirabayashi M, Inoue K, Tanaka K, Nakadate K, Ohsawa Y, Kamei Y, Popiel AH, Sinohara A, Iwamatsu A, Kimura Y, Uchiyama Y, Hori S, Kakizuka A (2001) VCP/p97 in abnormal protein aggregates, cytoplasmic vacuoles, and cell death, phenotypes relevant to neurodegeneration. *Cell Death Diffe* 8:977-84

Muller JM, Deinhardt K, Rosewell I, Warren G, Shima DT (2007) Targeted deletion of p97 (VCP/CDC48) in mouse results in early embryonic lethality. *Biochem Biophys Res Commun* 354:459-65

Weihl CC, Miller SE, Hanson PI, Pestronk A (2007) Transgenic expression of inclusion body myopathy associated mutant p97/VCP causes weakness and ubiquitinated protein inclusions in mice. *Hum Mol Genet* 16:919-28

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