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IBMPFD Educational Information – For Non-Genetics Healthcare Providers

What is IBMPFD?

IBMPFD stands for **I**nclusion **B**ody **M**yopathy associated with **P**aget's disease of bone and/or **F**rontotemporal **D**ementia. IBMPFD is a rare adult onset genetic disease caused by any one of several possible genetic changes (mutations) in a gene called Valosin Containing Protein (VCP or p97). The clinical features include one or a combination of the following: myopathy, early onset Paget's disease of bone, and premature frontotemporal dementia. IBMPFD is progressive and death typically occurs in the 50s and 60s from respiratory and cardiac failure.

Clinical Diagnosis of IBMPFD

People with IBMPFD may have one or a combination of the three main features. Symptoms are generally first recognized by doctors in the 40s or 50s, although subtle manifestations may be noticed by the patient in their 20s or 30s. Symptoms may include:

1) **Myopathy**: Muscle atrophy is usually progressive, and most people will eventually need to use a wheelchair and other mechanical aids for mobility. The proximal muscles are usually affected before the distal muscles in the legs and arms. The myopathy may clinically resemble limb-girdle (LG) or facio-scapulo-humeral (FSH) muscular dystrophy. Myopathy can also affect the cardiac and respiratory systems, leading to earlier death. Family studies have found myopathy in 87 - 92% of people with IBMPFD.
   Myopathy Evaluation: Serum CK concentration, electromyogram, and skeletal muscle histology.

2) **Paget's disease of bone** (PDB): Paget's disease is caused by problems with bone turnover, meaning that there are irregularities with the normal process of bone break-down and replacement. Symptoms of PDB include bone pain, localized bone enlargement, deformation of the long bones, and deafness from eighth-nerve compression. Family studies have found PDB in 51-57% of people with IBMPFD, usually with an earlier onset (mean age of 42) than is seen with isolated PDB (mean age of 59 years in those without family history).
   PDB Evaluation: Serum alkaline phosphatase concentration, urine concentrations of pyridinoline and deoxypyridinoline, and skeletal radiographs or radionuclide scan.

3) **Frontotemporal dementia** (FTD) that affects reasoning, personality, and language. Memory is relatively preserved until the later stages of the disorder. In family studies approximately 30% of people with IBMPFD have FTD.
   FTD Evaluation: comprehensive neurological assessment and imaging.

Approximately 12% of people with IBMPFD are affected with all three features listed above. 50% of affected people have two of the features, 30% have apparently isolated myopathy, and 8% have apparently isolated PDB or FTD.

Treatment and Therapy

Unfortunately, there is no cure for IBMPFD because the mutation is present in every cell of the body and it is not currently possible to change a mutation in every cell. Management of the disease involves an interdisciplinary healthcare team that includes Genetics, Cardiology, Neurology, physical therapy, and psychosocial support for patients and caregivers. There are treatments to help lessen, delay, or eliminate some of the symptoms of PDB. There are also some therapies for maintaining quality of life for as long as possible and slowing the rate of decline.

1) **Myopathy:** There is no direct treatment for myopathy. Quality of Life therapies include using assisted living devices like wheelchairs, walkers, canes, toilet lifts, and lift chairs as respiratory aids. Patients should have regular echocardiograms to monitor for signs of cardiomyopathy. Supportive therapies include physical therapy and stretching exercises to promote mobility and general physical health. For example, these exercises might reduce susceptibility to breathing problems and pneumonia.

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Treatment and Therapy *(continued)*

2) **Bone:** Oral bisphosphonate treatment is effective at rebuilding normal bone and treating the pain associated with the condition. Some drug treatments have the potential to significantly eliminate the symptoms of PDB (e.g. Reclast).

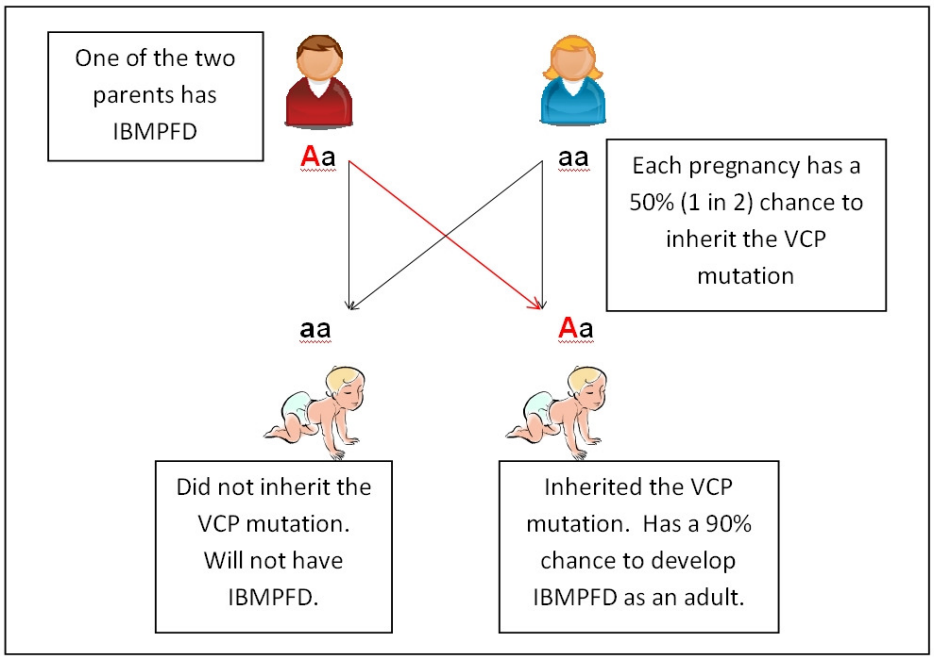
3) **Brain:** There is no medication that has been approved specifically to treat FTD. People with IBMPFD should meet with a neurologist to discuss FTD management which might include therapies to mitigate symptoms or off-label medications.

4) **Other:** Social and emotional support systems are often extremely valuable for patients, their caregivers, and family members.

IBMPFD Inheritance and Genetics

Valosin Containing Protein (VCP) is the only gene causing IBMPFD that has been identified, but others may be found in the future. Among people who meet the clinical criteria described above, VCP mutations will be identified in approximately 70% of cases. The gene is located on chromosome 9 and is thought to be involved in a number of essential cellular activities.

Each cell in the body has two copies of the VCP gene. IBMPFD is an autosomal dominant disorder, meaning that one mutation in either copy of VCP is sufficient to cause the disease. If a parent has a VCP mutation, then each of his or her children will have a 50% probability (1 in 2 chance) to inherit the mutation.



The known VCP mutations are highly penetrant, meaning that approximately 90% of people who have a mutation will become affected with one or more symptoms of the disease. Variability in severity and age of onset will be seen even among members of the same family. For example, the disease may progress at different rates, some family members may have PDB while others do not, and different family members may have different secondary symptoms. Researchers do not completely understand yet why there can be such a difference in symptoms between people with the same mutation of the VCP gene. These differences may be caused by the effects of other genes that interact with VCP, differences in lifestyle, or other genetic factors.

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IBMPFD Inheritance and Genetics *(continued)*

Most (80% or 8 out of 10) affected people also have an affected parent, but 20% (2 out of 10) of people with IBMPFD do not have anyone else in their family with the disease. It is most likely that these individuals have a new mutation that was not present in previous generations.

Purpose of VCP Genetic Testing

IBMPFD has often been misdiagnosed clinically. Finding a mutation in VCP is the only conclusive way to establish an accurate diagnosis. An accurate diagnosis gives information and opportunities for:

- Screening guidelines for potentially affected systems (e.g. echocardiograms, PDB evaluation), permitting earlier treatment of these conditions
- Lifestyle changes for the patient (e.g., changes in diet, nutrition, and exercise)
- The choice to participate in research to learn more about IBMPFD
- Accurate recurrence risk counseling or identification of at-risk family members
- Presymptomatic testing for family members who are at risk
- Prenatal testing through amniocentesis or chorionic villus sampling (CVS)
- Preimplantation genetic diagnosis (PGD) in conjunction with in vitro fertilization (IVF) for families who wish to have only pregnancies that do not carry a familial VCP mutation. The sperm and egg are joined in a laboratory and the embryos have the VCP genetic test. Only embryos that do not have the familial mutation are transferred to the mother to carry to term.

Risks of VCP Genetic Testing:

Referrals to a geneticist or a genetic counselor are strongly recommended for presymptomatic patients. These patients require psychological preparation before testing, including in depth discussion of their reasons for testing and how both positive and negative results would affect their lives. Discussing the implications of testing will allow the patient to make a fully informed decision about whether or not to proceed.

Genetic privacy and discrimination issues have been a large area of concern, especially among people seeking presymptomatic genetic testing. The passage of the Genetic Information Nondiscrimination Act (GINA) of 2008 now provides protection against health insurance and employment discrimination based on genetic information. However, this law does not cover life, disability, or long term care insurance and does not apply to members of the military. It is also still relatively new and has not yet been tested in court, so the extent of GINA's protection is still not well established. Patients should still think carefully about how their DNA test result might impact their employment and insurance. In addition, it is important to allow sufficient time before ordering the test for the patient to make any necessary financial or insurance arrangements. A genetics professional can help to guide your patient through this process.

Ordering the VCP test and Billing Information

There are a number of options to order genetic testing of VCP. Physicians can order full sequencing of the VCP gene or targeted sequencing of the exons where mutations are most frequently found. Mitomed Diagnostic Laboratory accepts only institutional or cash payment. Third party payments will not be accepted. Please see the Mitomed website for requisitions and more detailed information about ordering: http://mitomed.bio.uci.edu.

VCP Gene Testing Options

5006: Full sequencing of the VCP gene

Price: $1719 for full sequencing of all exons
$1547.10 if stepwise testing is ordered with exon 5 screen (total=1887.80)
$1317.90 if stepwise testing is ordered with exon 4 screen (total =2120.10)
CPT codes: 83891, 83898, 83894, 83904x2, 83912

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VCP Gene Testing Options *(continued)*

5007: Exon 5 screening: 63% of identified mutations have been found in exon 5.
Price: $343.80
CPT codes: 83891, 83898, 83894, 83904x2, 83912

5008: Screen of the commonly mutated exons: All known mutations are in exons 3, 5, 6, and 10 of VCP.
Price: $802.20 USD
CPT codes: 83891, 83898x5, 83894, 83904x10, 83912

9001: Testing of a known familial mutation
Price: $326.61 USD
CPT codes: 83891, 83898, 83894, 83904x2, 83912

Reproductive Testing: Mitomed does not offer prenatal testing or Preimplantation Genetic Diagnosis (PGD), but these tests can be coordinated with other centers offering custom testing. Mitomed does not charge to coordinate reproductive testing for mutations identified in our laboratory. Prenatal testing can be arranged through GeneDx or another laboratory chosen by the patient or doctor. GeneDx charges $1500 USD for prenatal testing and requires 8 weeks advance notice to set up the test before the prenatal sample is collected.

Sample Requirements and Turnaround Time

VCP testing is performed on 3-10 cc of blood drawn in a lavender top (EDTA) tube. Please ship samples by overnight courier at room temperature as soon as possible after they are drawn. If the specimen cannot be sent immediately, please store it in the refrigerator at 4 ^{o}C. Turnaround time is within 3 weeks for each tier of testing ordered.

Interpreting VCP Results

1) **Positive:** A positive result means that a mutation in VCP known to be associated with IBMPFD has been identified in the patient. A positive result may confirm the diagnosis in a person who meets clinical criteria or it may provide a pre-symptomatic diagnosis for an unaffected individual. If an unaffected individual has a positive result, there is a 90% chance that he or she will experience one or more of the features of IBMPFD. Onset of symptoms is age-dependent.

2) **Negative:** A negative result means that no mutation has been identified in the exons examined. This result is interpreted differently depending on the purpose of testing.

   a) Affected Individual: Mutations will be found in approximately 70% of people who meet clinical criteria for IBMPFD. The other 30% of clinically affected people may have mutations that the test is not designed to detect. Or they may have mutations in another gene that has not yet been identified. Please feel free to contact the lab to discuss options. Your patient may wish to participate in research studies.

   b) Unaffected individual in a family with a known mutation: If a family mutation in VCP has already been identified, a negative result means that the person does not have the genetic change that causes IBMPFD.

   c) Unaffected individual in a family without a known mutation: If there is a strong clinical presentation and family history consistent with IBMPFD but no mutation has been identified, then a negative result decreases the chance that the patient will be affected with IBMPFD. However, the result is not as meaningful if a familial mutation has not been found. It is possible that the family may have a type of mutation in VCP that the test is not designed to detect. Or they may have a mutation in another gene that has not yet been identified.

3) **Variant of Unknown Significance:**

A variant of unknown significance (VOUS) is a change in the VCP gene that has not previously been associated with IBMPFD. This result means that no data exists to support whether or not the variant is benign or a mutation that

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Interpreting VCP Results *(continued)*

can cause IBMPFD. The lab evaluates the variant to determine the type of mutation, amino acid change, level of conservation, etc. and will provide this information in the report. Your patient may wish to participate in research studies to further investigate the finding.

Resources for Healthcare Professionals

If you would like more detailed information about IBMPFD, please consult the IBMPFD profile in GeneTests (www.genetests.org). The profile gives a more complete discussion of the diagnosis, treatment and management of IBMPFD.

Genetic Counseling is recommended to explain the implications of a result to patients and their families. To find a genetics professional in your area you may wish to consult: GeneTests (www.genetests.org) or the National Society of Genetic Counselors (www.nsgc.org).

Please also feel free to contact Mitomed Diagnostic Laboratory with questions about testing. Please call 949-824-1886 or email mdl.lab@uci.edu. You can also visit our website for more information about the laboratory: http://mitomed.bio.uci.edu

Resources for Patients

David Sweetman, a patient advocate with IBMPFD, maintains a website: www.ibmpfd.com. The website offers a message board, contact information for research groups, and a variety of other useful information for patients, caregivers, and researchers.

IBMPFD is not yet recognized by the Muscular Dystrophy Association (MDA); however, many MDA centers accept persons with IBMPFD to their programs. The muscle related symptoms and daily challenges are similar to those experienced by people with muscular dystrophy or IBM (Inclusion Body Myocitis) a disease recognized by MDA. Patients may wish to visit their website at www.mdausa.org or to call them at 1-800-FIGHT-MD (344-4863).

Research studies may be available through the research laboratory of Virginia Kimonis, MD, MRCP. The research laboratory can be reached at http://mammag.web.uci.edu/bin/view/MAMMAG/VirginiaKimonis or 714-4562942.

References:

- Nat Genet. 2004 Apr;36(4):377-81. Epub 2004 Mar 21. Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein.
- GeneReview on IBMPD at www.genetests.org

Authors:

This material was written collaboratively by Mitomed Diagnostic Laboratory, David Sweetman, and the research laboratory of Dr. Virginia Kimonis.

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