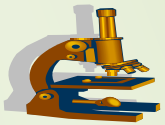

Global Microarray Analysis in VCP Disease Patients

Dr. Angèle Nalbandian has been working on VCP-associated neurodegenerative diseases including Inclusion Body Myopathy associated with Paget's disease of the bone and Frontotemporal Dementia (IBMPFD) and more recently amyotropic lateral sclerosis (ALS) in the Kimonis Laboratory. IBMPFD is a progressive, and ultimately a lethal condition with an onset usually in 30s to 40s, showing autosomal dominant inheritance. Affected individuals die from progressive muscle weakness, cardiac and respiratory failure typically in their 40s to 60s. It causes weakness and atrophy of the skeletal muscles of the pelvic and shoulder girdle muscles in 82% of patients, the main age of presentation being 42 years. Muscle weakness progresses to involve other limb and respiratory muscles, and cardiac failure and cardiomyopathy have been observed in later stages. Our initial global differential microarray analysis was performed with 10 muscle samples (3 controls and 7 affected individuals). We characterized the genes that were differentially expressed in the patients' muscle using gene pathways. These pathways are currently being analyzed for different patterns of RNA and protein expression specifically related to the ubiquitin proteasome and autophagy degradative pathway and will provide significant insight into the mechanisms responsible for VCP-associated diseases. We are currently analyzing the genes involved in these signaling pathways to design novel treatment strategies for our patients.

Nalbandian A, Ghimbovschi S, Radom-Aizik S, Dec E, Vesa J, Martin B, Knoblach S, Smith C, Hoffman E, Kimonis VE. **Global Gene Profiling of VCP-associated Inclusion Body Myopathy.** Clin Translational Science. 2012 Jun;5(3):226-34.

Clinical Data Updates

Dr. Manaswitha Khare, a physician with Kimonis laboratory since 2011, is working on the clinical studies of VCP- associated disease. There are >25 mutations in the VCP gene that have been identified to date. She is currently working on delineating the association between different genetic subtypes and various clinical features. Approximately 10-15% of individuals have amyotropic lateral sclerosis (ALS) and some individuals/families have been identified with Parkinson's disease.

If you have any medical updates for Dr Kimonis please contact her or members of her team. If you are having surgery please consider donating some tissue such as muscle, bone etc.

The manuscript entitled Genotype-Phenotype studies of VCP-associated Inclusion Body Myopathy with Paget Disease of Bone and/or Frontotemporal Dementia has been submitted to Clinical Genetics journal and is pending publication. She will also be participating in the American Society of Human Genetics conference in San Francisco to present her research work.

The Kimonis lab has maintained a database of all the patients recruited for its studies and Dr. Kimonis has continued contact with them. She has collected autopsy samples and developed standards of care for genetic counseling for presymptomatic patients.

Our pilot comprehensive clinical studies at UC Irvine have included detailed analysis in individuals with VCP mutations and controls including first degree unaffected relatives. These studies comprise of extensive tests over two days including history, physical exam, blood work, EMG, DEXA scan, bone scan, MRI, and muscle biopsy. Dr. Khare is also currently working on analyzing data on the individuals who participated in the UC Irvine IBMPFD Natural History study. Ultimately, we are hoping that our research will achieve novel therapeutic targets to benefit our patients with VCP disease.

Nalbandian A, Donkervoort S, Dec E, Badadani M, Katheria V, Rana P, Nguyen C, Mukherjee J, Caiozzo V, Martin B, Watts GD, Vesa J, Smith C, Kimonis VE. (2011) **The Multiple Faces of Valosin-Containing Protein-Associated Diseases: Inclusion Body Myopathy with Paget's Disease of Bone, Frontotemporal Dementia, and Amyotrophic Lateral Sclerosis.** J Mol Neurosci. Nov;45(3):522-31. Epub 2011

High Fat Diet Rescues the Homozygous Mouse

We have crossed our VCP mice to produce mice with two mutations. These mice typically die by 21 days. We have rescued the mice by feeding a diet high in soya oil. The diet has high amount of linoleic acid (omega 6 oil) and oleic acid (omega 9 oil). We are in the process of refining this observation for the purpose of developing a treatment for patients with VCP disease.

Mouse Model with IBMPFD

The Kimonis Laboratory has generated a Neomycin cassette-free novel VCPR155H/+ knock-in mouse as a true model of the disease, which expresses the mutant VCP allele at an endogenous level without interference from the Neomycin cassette. The VCPR155H/+ mouse model, demonstrates muscle weakness, typical histopathology, and progressive accumulation of TDP-43, ubiquitin, and LC3 in muscle, resembling the onset in humans in the 30s-40s. The VCPR155H/+ mice show milder, but typical muscle and brain pathology and mild increase in the TDP-43, ubiquitin, and LC3 pathology. Additionally, the spinal cords of these animals demonstrate neuronal atrophy and astrocyte proliferation, and electrodiagnostic studies reveal a neurogenic pattern seen in ALS. This VCPR155H/+ knock- in mouse can be exploited for the development of novel strategies and treatments without potential interference from the Neomycin cassette.

Dr. Nalbandian is currently working on exercise physiology regimens in animal models to further understand the effects of exercise in VCP-associated disorders. She recently attended the Neuromuscular Colloquium in Newport Beach, CA and will be attending the American Society of Human Genetics Conference in San Francisco, CA in November to present her research. These are very exciting times in the Kimonis Laboratory as we are making groundbreaking discoveries and gaining novel insights into the mechanisms of these diseases in order to develop therapeutic agents for our patients. We are truly grateful for all our patients and their selfless support and dedication of our research studies.

Nalbandian A, Llewellyn K, Badadani M, Yin H, Nguyen C, Katheria V, Watts G, Mukherjee J, Vesa J, Caiozzo V, Mozaffar T, Weiss J, Kimonis VE. (2012) A **Progressive Translational Mouse Model of Human VCP Disease: The VCP R155H/+ Mouse.** Muscle Nerve (in press).

Badadani M, Nalbandian A, Watts GD, Vesa J, Kitazawa M, Su H, Tanaja J, Dec E, Wallace DC, Mukherjee J, Caiozzo V, Warman M, Kimonis VE. (2010) **VCP associated inclusion body myopathy and paget disease of bone knock-in mouse model exhibits tissue pathology typical of human disease.** PLoS ONE 5. Oct 5;5(10). pii: e13183.

Yin H, Nalbandian A, Hsu C, Li S, Llewellyn K, Mozaffar T, Kimonis VE, Weiss J. (2012) **A mutant valosin-containing protein (VCP) gene knockin mouse model of ALS** Cell Death and Disease (in press).

Significant Events in the Kimonis Lab

- ***March 2011***: Awarded The Dean's Triumvirate Grant: Therapeutic targets for treatment of Hereditary Inclusion Body Myopathy (IBMPFD).
- ***September 2011***: Dr. Nalbandian presented a poster on her research in VCP disease at the 61st annual American Society of Human Genetics meeting, Montreal, Canada.
- ***March 2012***: Awarded grant from the National Institute of Health: High-fat diet rescues lethality of homozygous knock-in R155H VCP myopathic.
- ***May 2012***: Kimonis lab members presented three posters on our research on VCP and MTAP diseases at the 2nd Annual Neuromuscular Colloquium: Current and Future Therapeutic Approaches in Neuromuscular Diseases, Newport Beach, CA.
- ***June 2012***: Dr. Kimonis was awarded the Outstanding Mentor Award from the University of California, Irvine's Institute for Clinical and Translational Science.

MTAP Disease (Canada family)

Dr. Llewellyn has started working on an autosomal-dominant disease called Diaphyseal medullary stenosis with malignant fibrous histiocytoma (DMS-MFH). Patients with this syndrome suffer from bone fracturability with poor healing, myopathy, bone cancer, premature graying and soft skin. We now know that mutations within the gene MTAP are the cause of this disease. Scientists think that this is through dysregulation of the newly discovered MTAP splice variants. She focuses on characterizing the myopathy and understanding how dysregulation of the MTAP splice variants could cause this disease. She has recently found that some of the proteins affected in IBMPFD, seem to be affected within this disease as well. With similar phenotypes it is likely that the same pathways affected by IBMPFD are affected by DMS-MFH. Hopefully, we can increase awareness and interest to help find a viable treatment or cure for DMS-MFH.

Camacho-Vanegas O, Camacho SC, Till J, Miranda-Lorenzo I, Terzo E, Ramirez MC, Schramm V, Cordovano G, Watts G, Mehta S, Kimonis V, Hoch B, Philibert KD, Raabe CA, Bishop DF, Glucksman MJ, Martignetti JA. **Primate genome gain and loss: a bone dysplasia, muscular dystrophy, and bone cancer syndrome resulting from mutated retroviral-derived MTAP transcripts**, Am J Hum Genet 2012 Apr 6;90(4):614-27.

VCP Exercise Study

We are planning a study that will investigate the influence of exercise on muscle strength in VCP Disease. It is an exercise regimen conducted three times a week over the course of 12 weeks. The routine will consists solely of an exercise called knee extensors. This exercise can be performed at your local gym or your home with ankle weights. At each training session you will do three sets of ten knee extensors. Each week the amount of weight used will be increased. You will be asked to keep a log following each training program and rate your level of fatigue. At the start and end of the 12 weeks of training we will ask you to visit UC Irvine so we can conduct an analysis using a battery of tests consisting of strength measurements, MRI, and muscle biopsy.

Study Participation: It would be very helpful if more families participated in our studies. If you know of others who may be interested, please contact: **Study Coordinator Marie Wencel:** (949) 824-0521

Organ Donation:

We are actively seeking organ donations to further our research and find a cure for IBMPFD. Please contact Dr. Kimonis at (949) 824-0571 if you wish to donate your body.

Please contact us if you can donate samples of muscle, bone, or other tissue at the time of planned or emergency surgery.

Please visit our website at: http://mammag.hs.uci.edu/foswiki/bin/view/MAMMAG/InclusionBodyMyopathyAssociatedWithPagetSDiseaseOfBoneAndFrontotemporalDementia or Google 'Kimonis laboratory'

Funding: We have limited funding from the NIH and MDA. To be able to develop cures for genetic disorders, your help is essential. Please consider organizing fundraisers and donating to our research program at:

www.uadv.uci.edu/IBMPFDMyopathyPagetAndDementiaResearch

Please notify Dr. Kimonis when you have made a donation

Donate Today!!

The Kimonis Laboratory, University of California Irvine
101 The City Drive South, ZC4482, Orange CA 92868
Tel: (949) 824-0571, Fax: (949) 824-0171, Pager (714) 506-2603
Email: vkimonis@uci.edu

More information on IBMPFD, as well as support group information, can be found at http://www.ibmpfd.com.

UNIVERSITY of CALIFORNIA • IRVINE

Newsletter

Summer 2012

From left to right: First Row: Christina Su, Marie Wencel, Dr. Angele Nalbandian, Sharis Shamirian, Dr. Katrina Llewellyn, Kimberly Lank. Second Row: Veeral Katheria, Vincent Pan, Armen Pezeshkian, Dr. Manaswitha Khare, Christopher Nguyen, Dr. Virginia Kimonis

We are pleased to send you our Fourth Annual Newsletter as an update on our research studies. In the past year, we have published multiple articles on our research in VCP disease. Progress has been made in making a progressive translational mouse model of Human VCP disease, performing global differential microarray analysis, furthering the research of MTAP gene, and planning a new exercise study. We hope these research efforts will help us develop novel treatment strategies for our patients.