

# NRRC *newsletter*

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News & Featured Research of the Neuroscience Research Center

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## A view of brain degenerative diseases from the lens of Huntington's

By Sheng Zhang, Ph.D.



Zhang

*such as synaptic dysfunction and abnormal protein deposits (e.g., plaques and tangles), these diseases often affect different regions and preferentially destroy different neuronal cell types in the brain. Among these diseases, HD represents a relatively uncomplicated example in that its genetic cause is rather simple and unique as the disease pathology arises from an abnormal expansion of a CAG tri-nucleotide repeat in a single gene called Huntingtin. Yet, even for this genetically well-defined disease, the cellular and molecular events underlying its pathogenesis are still far from clear. HD and other human brain diseases can be effectively modeled in various experimental organisms such as in the invertebrate Drosophila, commonly known as the "fruit fly". Knowledge learned from HD could help shed light on tackling this and other more complicated brain degenerative disorders.*

With improved healthcare as well as a better understanding of more fatal diseases such as cancer and cardiovascular conditions, our society is enjoying an unprecedented longer life expectancy. However, this welcome benefit also exposes a pressing threat to the well-being of our society: the looming social and economic burdens from age-related brain degenerative diseases, including Alzheimer's (AD), Parkinson's (PD), and others. As these debilitating diseases progress through a relatively extended time course (10-20 years), they gradually destroy the mental and physical capabilities of the victim, exacting a heavy emotional and financial toll on the family and extracting a disproportionately high cost to the healthcare system.

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## Studying synapse development and function in fruit flies

By: Kartik Venkatachalam, Ph.D.



Venkatachalam

*synaptic development and function using fruit flies as a model organism.*

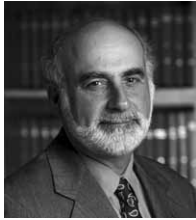
*Abstract: The capacity of the nervous system to process information depends upon an intricate network of neurons connected to each other via synapses. Alterations in pathways regulating synaptic growth and function occur in several neuropsychiatric diseases. Here, I describe the approach we are taking in my laboratory to identify evolutionarily conserved genes that determine*

"Who am I?" This existential question has fascinated both scientists and philosophers for millennia. In the contemporary post-genomic era, answers are finally beginning to emerge. The prevailing theory is that we are defined by our genes. Personalities, behavior, and even political mindsets have been linked to an individual's genetic make-up. This concept is further supported by the fact that identical twins with the same genetic make-up display a remarkable convergence in several aspects of their lives. But is this the whole picture? Are we really just a collage of our genes? What about our memories, thoughts, fears, ambitions, and life experiences—the unique aspects of us? Arguably these factors define us a lot more than the genes we inherit from our parents. It appears that although genes set the stage, the actual process of thought and personality encoding is conducted by components of the nervous system. However, from this simple statement emerges a much larger and daunting enigma: how does the brain actually store all this information, and evoke higher order concepts like con-

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# NRC Activities for 2012-2013

From the director, John H. Byrne, Ph.D.



As we commence our third decade, the UTHealth Neuroscience Research Center (NRC) continues to foster the neurosciences within UTHealth as well as initiate new partnerships. Being located in the largest medical center in the world has its advantages. We are surrounded by 54 member institutions that include hospitals, research institutes, medical, nursing and dental schools, private not-for-profit health-related foundations, a high school for health professionals and many other diverse organizations. The past few years have resulted in several exciting new collaborations.

The annual neuroscience Poster Session is one of our longest running events at the NRC. This informal event that began in 1993 was originally designed to promote scientific exchange and collaboration among research scientists, postdoctoral fellows, graduate and medical students within UTHealth. However in 2011, for the first time, the participation was expanded to include graduate students from the Department of Psychology at Rice University, and in 2012, participation was expanded further to include also graduate students and postdoctoral fellows from the Department of Neuroscience at Baylor College of Medicine. 2012 marked our largest poster session to date with 75 poster presentations, 35 judges and over 125 people in attendance. Topics presented included research progress on drugs and behavior, visual and sensory processing, learning and memory, theoretical and computational studies, language, spinal cord injury, technology, and disease. Cash prizes for first, second and third place were awarded to the top graduate student and postdoctoral fellow poster presenters. This highly-successful event would not have been possible without the enthusiastic support of Dora Angelaki, Chair of Neuroscience at Baylor, and Jim Dannemiller, Chair of Psychology at Rice.

Joint efforts have been particularly strong in the fields of computational, systems and cognitive neuroscience. Two years ago the UTHealth Department of Neurobiology & Anatomy started hosting seminars jointly with Rice and Baylor. In addition, the Neuroscience Graduate Program, which is part of the UTHealth Graduate School of Biomedical Sciences, created four program tracks to allow students to focus their doctoral research experience. An important strength of this concept is that many of these tracks are part of multi-institutional programs, allowing students the opportunity to work with a larger group of faculty and take additional higher level courses specific to their area of interest. For example, the Systems and Cognitive Neuroscience track is a joint program with the Rice Department of Psychology Systems and Cognitive Neuroscience Research Interest Group. Students in this program are able to focus their studies on the highest level of cognitive and systems neuroscience, including language, cognition, memory, and visual perception. Many of these courses are jointly taught by faculty from UTHealth and Rice and cross-listed at both institutions. Two

courses "Introduction to Cognitive Neuroscience" (directed by Anne Sereno, UTHealth) and "Cognitive Neuroscience" (co-directed by A. Cris Hamilton, Rice and Anne Sereno, UTHealth) have been particularly successful cornerstones of the joint program. The inter-institutional spirit of these courses have also benefited from guest lectures by Wei Ji Ma and Saumil Patel from Baylor College of Medicine.

In fact, these institutions have been collaborating for many years on educational programs, in particular in the field of computational neuroscience. The Theoretical and Computational Neuroscience track is another example of inter-institutional collaboration. Students are encouraged to explore both the theoretical and experimental aspects of computational neuroscience and often have two mentors, a theorist and an experimentalist. Two required courses of Theoretical Neuroscience are coordinated by Harel Shouval and are part of the graduate curricula of Rice, Baylor, UTHealth and the University of Houston. In addition, these four institutions are part of The Gulf Coast Consortia (GCC), which also includes The University of Texas Medical Branch at Galveston and The University of Texas M.D. Anderson Cancer Center. The goal of the GCC is to construct interdisciplinary research and training programs with a focus on the computational and mathematical aspects of the biological sciences. This includes computational neuroscience courses, seminars and journal clubs, workshops and retreats. In addition, the GCC research programs support over 500 faculty and their collaborative work in areas such as theoretical and computational neuroscience, and bioinformatics to name a few.

An exciting new development is the proposal for the creation of an undergraduate minor in Neuroscience at Rice University. A Steering Committee consisting of myself, Dora Angelaki and David Dickman from Baylor, and Rice University faculty Behnaam Aazhang (Electrical and Computer Engineering), Janet Braun (Biochemistry and Cell Biology), Steven Cox (Computational and Applied Mathematics), Suzanne Kemmer (Linguistics), Casey O'Callaghan (Philosophy), and James Pomerantz (Psychology) has recommended a curriculum that if approved could be implemented within the very near future. The proposed curriculum will allow Rice undergraduates the opportunity to participate in research at UTHealth and Baylor, as well as enroll in courses for credit. It will also provide an opportunity for UTHealth and Baylor graduate students and postdoctoral fellows to serve as Teaching Assistants in the new courses that will be developed.

In addition to inter-university collaborations, the NRC has made a strong effort to form meaningful relationships with high school programs in the local community. NRC members and students have taught special neuroscience courses in elementary and high school classrooms and we have also hosted high school students for laboratory tours. In the upcoming year, we look forward to reaching out and working with more Houston institutions at all levels of research and education.

# news & information

## Awards

### Grants

**Michael Beierlein**, Assistant Professor, Department of Neurobiology and Anatomy, received a 5-year R01 from the National Institute of Neurological Disorders and Stroke (NINDS) entitled "Synaptic Integration in Neurons of the Thalamic Reticular Nucleus".

**John H. Byrne**, Professor and Chair, Department of Neurobiology and Anatomy, received a 5-year R01 from the National Institutes of Health to study computational and empirical approaches to designing novel training and pharmacological protocols that rescue cognitive defects.

**Raymond Grill**, Assistant Professor, Department of Integrative Biology and Pharmacology, received three research grants this year. Two grants from the Department of Defense will study 1) the blood-testis-barrier and male sexual dysfunction following spinal cord injury, and 2) targeted riluzole delivery by antioxidant nanovectors for treating amyotrophic lateral sclerosis. In addition, a grant from Mission Connect will allow him to study enhancing recovery of locomotor function in chronic SCI by combining COX/5LOX-inhibition with rehabilitation.

**Giridhar P. Kalamangalam**, Assistant Professor, Department of Neurology, received a 5-year NIH K23 award to develop advanced MR imaging techniques for epilepsy.

**David W. Marshak**, Professor, Department of Neurobiology and Anatomy, received a new subcontract from the National Eye Institute to discover the "connectome" of the primate retina (Principal Investigator, Robert E. Marc)

**Stephen C. Massey**, Professor and Elizabeth Morford Chair, Department of Ophthalmology and Visual Sciences, in collaboration with Laura Frishman at the University of Houston, College of Optometry, received an NIH T32 grant to support three graduate students and one post-doctoral fellow in the Houston area Vision Training Program. He also received an award from the NIH Office of the Director, Shared Instrumentation Grant Program, to obtain a new confocal microscope for the Vision Core Grant confocal facility.

**Dianna M. Milewicz**, Professor and Director, Department of Internal Medicine, has received an NIH R01 in March and a NIH Program Project grant award in August. She also received a grant to make a mouse model of Moyamoya disease due to mutation in PCNT.

**Ponnada Narayana**, Professor, Department of Diagnostic and Interventional Imaging, received an NIH/NINDS grant for the analysis of multi-center MRI data to investigate the relation between atrophy and lesion activity in Multiple Sclerosis.

**Jair Soares**, Professor and Chair, Department of Psychiatry and Behavioral Sciences, received an NIH grant to study the role of heritability on key brain abnormalities involved in causation of bipolar disorder.

**Nitin Tandon**, Associate Professor, Department of Neurosurgery, received two grants from NINDS to study 1) the representation and binding of spatial and temporal episodic memories in human hippocampus, and 2) the role of SV2A phosphorylation in epilepsy.

### Awards

The **Neuroscience Research Center** was selected by Mental Health America of Greater Houston for the "2012 Mental Health Makes A Difference Community Recognition" award for our annual event, Brain Night for Children. We are featured in a book on mental health in Houston, which can be downloaded at <http://www.mha-houston.org/files/223>, as well as in a gallery display at the Houston Public Library – Central Location. Brain Night would not be possible without our many loyal volunteers and the support from the Society for Neuroscience Chapter Grant.

**John H. Byrne**, Professor and Chair, Department of Neurobiology and Anatomy, received an Innovation in Health Science Education Award from The University of Texas Academy of Health Science Education for his work on *Neuroscience Online*, an electronic textbook for neurosciences.

**Leonard J. Cleary**, Professor, Department of Neurobiology and Anatomy, **Marianne T. Marcus**, UTHHealth School of Nursing, and **Henry W. Strobel**, Associate Dean for Faculty Affairs and Alumni Relations, received The University of Texas System Regents' Outstanding Teaching Award in recognition of faculty members at the nine academic and six health University of Texas System institutions who have demonstrated extraordinary classroom performance and innovation in instruction.

**Raymond Grill**, Assistant Professor, Department of Cell and Regulatory Biology, recently received three awards: Cell and Regulatory Biology Faculty Recognition award, New Investigator Development Program Mentor award, and The Jerry Johnston Andrew Spinal Cord Research Award.

**R. Andrew Harper**, Professor, Department of Psychiatry, and Medical Director of Harris County Psychiatric Center, was appointed to Distinguished Teaching Professor of the University of Texas System.

**Stephen C. Massey**, Professor and Elizabeth Morford Chair, received the Boycott Prize for achievement in retinal neuroscience at the 2012 Federation of American Societies for Experimental Biology (FASEB) Meeting on Retinal Neurobiology and Visual Processing.

**Dianna M. Milewicz**, Professor and Director, Department of Internal Medicine, was awarded by BioHouston at its Fourth Annual Lunch Celebrating Women in Science for demonstrating "extraordinary leadership in science and technology."

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## Publications

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Colorado R, Shukla K, Yuxiang Z, **Wolinsky JS**, **Narayana PA** (2012) Multi-task functional MRI in multiple sclerosis patients without clinical disability. *NeuroImage* 59:573-81.

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Gupta RK, Awasthi R, Rathore RKS, Verma A, Sahoo P, Paliwal VK, Prasad KN, Pandey CM, **Narayana PA** (2012) Understanding Epileptogenesis in calcified neurocysticercosis with perfusion MRI. *Neurology* 78:618-25.

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Kothmann WW, Trexler EB, Whitaker CM, Li W, **Massey SC**, **O'Brien J**. (2012) Nonsynaptic NMDA receptors mediate activity-dependent plasticity of gap junctional coupling in the AII amacrine cell network. *J Neurosci* 32:6747-59.

Li H, **O'Brien J** (2012) Regulation of gap junctional coupling in photoreceptors. In *Photoreceptors: Physiology, Types and Abnormalities*. Eds. E. Akutagawa and K. Ozaki. *Nova Science* (Hauppauge, NY).

Moller HU, Fledelius HC, **Milewicz DM**, Regalado ES, Ostergaard JR (2012) Eye features in three Danish patients with multi-systemic smooth muscle dysfunction syndrome. *Br J Ophthalmol* 96:1227-31.

Munot P, Saunders DE, **Milewicz DM**, Regalado ES, Ostergaard JR, Braun KP, Kerr T, Lichtenbelt KD, Philip S, Rittley C, Jacques TS, Cox TC, Ganesan V (2012) A novel distinctive cerebrovascular phenotype is associated with heterozygous Arg179ACTA2 mutations. *Brain* 135:2506-14.

O'Brien JJ, Chen X, Macleish PR, O'Brien J, Massey SC (2012) Photoreceptor coupling mediated by connexin36 in the primate retina. *J Neurosci* 32:4675-87 (Cover Picture).

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Vila A, Satoh H, Rangel C, Mills SL, Hoshi H, O'Brien J, Marshak DR, MacLeish PR, **Marshak DW** (2012) Histamine receptors of cones and horizontal cells in old world monkey retinas. *J Comp Neurol* 520: 528-543.

Vila A, Satoh H, Rangel C, **Mills SL**, Hoshi H, **O'Brien J**, Marshak DR, MacLeish PR, Marshak DW (2012) Histamine receptors of cones and horizontal cells in Old World monkey retinas. *J Comp Neurol* 520:528-43.

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Neurodegenerative diseases such as AD and PD often have a complicated etiology, as only a small portion of these cases are linked to a growing number of environmental and genetic factors, thus the cause for the majority of cases remains unknown. Such complexity further complicates the efforts in studying these diseases. In contrast, Huntington's disease (HD), another notorious brain disorder, stands out with a rather simple genetic picture: it is caused by a unique mutation, an abnormal expansion of a CAG tri-nucleotide repeat located near the N-terminus of a single gene called Huntingtin (Figures 1-3), thus offering a simpler case among these brain diseases.

HD is a dominantly inherited, fatal neurodegenerative disorder that affects at least 35,000 people in the United States alone, with another half million people at risk. Patients display abnormal involuntary movements such as chorea, as well as emotional symptoms and cognitive impairments leading to dementia. The symptoms of the disease usually become evident during middle age and progress more severely over time. Patients with HD usually die 10-15 years after disease onset. Pathologically, the disease causes neuronal death mainly in the mid-brain (corpus striatum region of the brain that is responsible for modulating motor movements), and to a lesser extent the cortical neurons that project to the striatum (Figure 1). Severe neuronal degeneration in an advanced stage of the disease can lead to around 30% loss in brain weight.

### CAG repeat, polyglutamine and HD pathogenesis: an intimate tangle

In healthy individuals, the number of CAG repeat in Huntingtin gene varies from 6 to 34. In contrast, in HD patients, it is always expanded to more than 35 repeats (Figure 2).

Importantly, the CAG repeat number is also a major determinant of the age when the symptoms of the disease begin to manifest: the longer the repeat, the younger the age of disease onset. This inverse correlation also underlies another genetic feature of the disease known as *anticipa-*

*tion*: it is observed that as the disease is passed from generation to generation, the symptoms become apparent at an earlier age. The molecular basis of this feature is due to the expansion of the CAG repeat in successive generations during parental germ-line transmission of the disease allele. Intriguingly, there exists a gender bias of this feature, as the expansion occurs more prominently when the HD alleles are inherited paternally.

As its pathological hallmark, abnormal aggregates (i.e., compact protein deposits) in cellular cytoplasm and nucleus are frequently observed in HD brains (Figure 1),

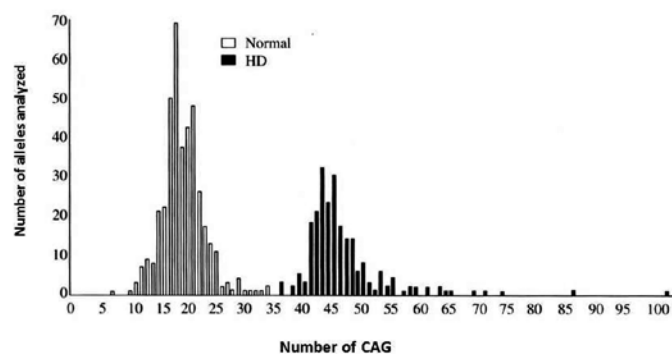


Figure 2. A study showing the distribution of CAG repeat number in HD patients and normal controls (*"Huntington's disease"*, page 119. 3rd edition. Edited by G Bates, P Harper & L Jones.)

similar to other brain disorders (e.g., plaques and tangles in AD and Lewy bodies in PD). Because codon CAG encodes amino acid glutamine (abbreviated as "Q"), the expanded CAG repeat in HD allele translates into an abnormally long glutamine tract (abbreviated as "polyQ") in the corresponding Huntingtin protein (Figure 3). It is believed that once polyQ length exceeds the pathogenic threshold (~34), mutated Huntingtin protein become prone to adopt an abnormal (i.e., mis-folded) conformation that resists clearance, gradually accumulating and forming larger aggregates. Indeed, the main components of the aggregates in HD include both the full-length and truncated N-terminal fragments of Huntingtin.

Strikingly, biochemically, the aggregation propensity of the mutated Huntingtin protein is also tightly linked to the length of polyQ track. For example, for protein products from the extensively studied Huntingtin exon1 where the CAG repeat resides, those with normal length of polyQ (<34) remains soluble in the cell while those with pathogenic length polyQ (> 36) form aggregates in an age-dependent manner. Further, the longer the polyQ length, the easier and faster these aggregates are to form.

### PolyQ confers a dominant toxicity

Studies in a number of animal- and cell-based dis-

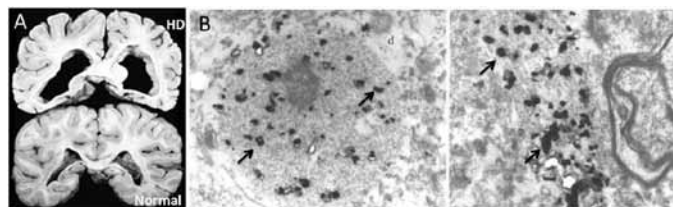
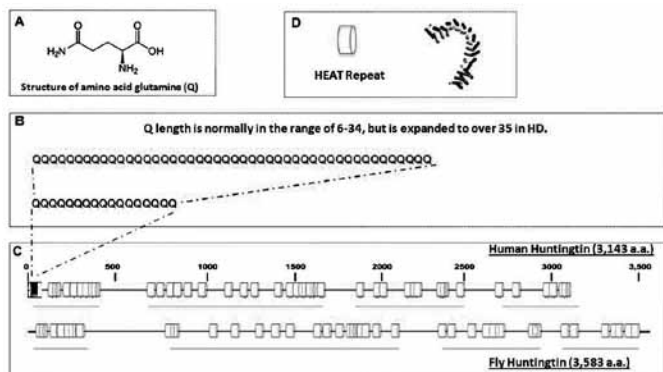


Figure 1. (A) The severe loss of mid-brain tissues in an HD case (top) as compared to an age-matched normal control (bottom) as revealed in brain pathological sections. (B) The presence of protein aggregates (dense black spots) in neurons from an HD adult brain as revealed by transmission electron microscopy (*"Huntington's disease"*, page 266. 3rd edition. Edited by G Bates, P Harper & L Jones.)



**Figure 3.**  
 (A) Schematic illustration of the structure of amino acid Glutamine (Q), which is encoded by the tri-nucleotide CAG.  
 (B) HD is caused by an abnormal expansion of the Glutamine tract (polyQ) located near the N-terminus of Huntingtin protein.  
 (C) Schematics of predicted secondary structures of human and *Drosophila* Huntingtin proteins. Both are composed mainly of HEAT (acronym for Huntingtin, elongation factor 3 (EF3), protein phosphatase 2A (PP2A), and the yeast kinase TOR1) repeats (represented as cylinder boxes in the diagram, also see D).  
 (D) Illustration of the proposed structure of the HEAT repeat, a ~40 amino acid long hairpin-like protein motif.

ease models have demonstrated that the expanded polyQ stretch confers deleterious novel functions to native proteins (i.e., a gained toxicity). For example, in transgenic mice and *Drosophila melanogaster* (commonly known as fruit flies), expressing an expanded polyQ tract either from mutant Huntingtin or in an unrelated protein such as Hypoxanthine-guanine phosphoribosyltransferase, or just expressing a polyQ tract alone, will almost always lead to a polyQ length-dependent neurodegenerative phenotype. But where does the toxicity come from?

**Unclear pathogenic mechanisms**

Given the intimate relationship of polyQ length with aggregate formation and HD pathogenesis, it is natural to hypothesize that the aggregates themselves are the toxic agent that kills the neurons. However, despite being a unifying pathogenic feature of most neurodegenerative diseases, the role of aggregates in neuronal degeneration remains highly controversial. On the basis of different studies, aggregates have been assigned diverse roles such as neurotoxic agents, beneficial factors, or simply by-products of the diseases.

In addition to aggregates, several other disease mechanisms have been proposed, including transcriptional dysregulation, abnormal cleavage of mutant Huntingtin and its subsequent nuclear accumulation, mitochondrial dysfunction, oxidative stress, proteasome malfunction, defective vesicle and axonal trafficking, among others. To date,

although there is a consensus that the expanded polyQ tract causes neuronal degeneration, the molecular mechanism underlying the gained toxicity remains unclear.

**Huntingtin, an enigmatic protein**

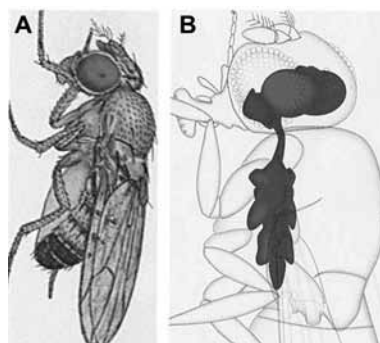
Normal Huntingtin is critical for vertebrate development and neuronal survival, as mice completely lacking Huntingtin die at very early embryonic stage, while reducing Huntingtin’s overall expression level or removing its presence in the postnatal brain leads to extensive brain defects and progressive neurodegenerative phenotypes.

At a molecular level, Huntingtin is predominantly a cytosolic protein of 3140 amino acids (a.a.) long. Despite this large size, no obvious functional domains have been identified in Huntingtin to suggest its normal cellular functions. Structural analysis of Huntingtin identified the presence of up to 40 HEAT repeat, a 40-a. a. long, anti-parallel helical structural motif of unknown function (Figure 3).

Since its identification in 1993, Huntingtin has been subjected to extensive studies and a large number of Huntingtin interacting partners have been reported, which lead to hypotheses that Huntingtin plays role in cellular endocytosis, synapse formation and activity, transcriptional regulation, vesicle trafficking and axonal transport, cell death, among several others. It is now generally believed that Huntingtin acts as a scaffold protein to integrate input from many cellular signals and coordinate cellular responses. But exactly how Huntingtin carries out its essential cellular and developmental roles remains to be elucidated.

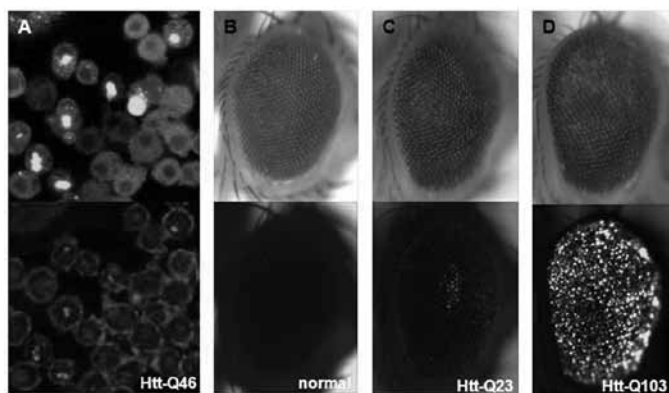
**The fruit fly, small insect, big promise**

Due to convenience factors including its small size and easy in-house culture, as well as its high fecundity and short reproductive cycle, *Drosophila* as an experimental organism has been subjected to thorough biological and genetic analyses for almost a century, and its development is one of the best understood (Figure 4). As such, this small insect has evolved into an excellent and also a favorite model organism for the functional analyses of many basic biological questions.



**Figure 4.**  
 Cartoon illustrations of (A) an adult fruit fly (*Drosophila melanogaster*) and (B) its internal central nervous system (highlighted tissues).

Other factors also contribute to the success of this simple invertebrate model. *Drosophila* is amenable to large-scale genetic screen and its sensitive genetic assays have led to the identification and validation of novel components in many cellular pathways. Further, many powerful experimental tools and *in vivo* assays for various cellular processes have been developed in this model, such as the use of various mutagenic methods, the ease to generate transgenic flies, as well as the UAS/GAL4 binary expression system for targeted overexpression of genes in specific tissues. Recently, genome-wide collections of UAS-based transgenic RNAi lines against every annotated gene in the *Drosophila* genome have also been established. These tools allow investigators to control exactly where and when during development the expression of a specific gene can be turned on or off.



**Figure 5**  
Formation of aggregates by mutant Huntingtin protein can be modeled and studied in (A) cultured *Drosophila* cells and (B-D) adult fly eyes. In this study, a green fluorescent label (eGFP tag) revealed Huntingtin protein (N-terminal exon 1 fragment). Double-labeling imaging of cultured *Drosophila* (S2?) cells expressing a mutant form of the Huntingtin protein containing 46 contiguous Glutamine repeats (Htt-Q46). Aggregates (bright dots in top picture) are evident in a significant number of cells. Staining for the cytoskeletal protein F-actin reveals the overall morphology of the S2 cells (bottom picture) as well as the sequestration of F-actin in these aggregates (bright dots in bottom picture). (B-D) Images of same adult fly eyes illuminated by (top panels) bright light to show the overall eye morphology; and by (bottom panels) fluorescent light to reveal the presence of the eGFP-labeled Huntingtin protein, respectively. No fluorescent signal in the eye of a normal fly (control) that does not express human Huntingtin protein. No clear aggregates in the eye of a transgenic fly that expresses normal human Huntingtin protein with 23 contiguous Glutamine repeats (Htt-Q23). Numerous aggregates (bright dots) in the eye of a transgenic fly that expresses mutant human Huntingtin protein with 103 contiguous Glutamine repeats (Htt-Q103).

## Our study on HD

Our lab focuses on studying the pathogenic mechanisms responsible for HD, in particular how formation of aggregates by mutant Huntingtin protein is regulated in a cell, and how normal Huntingtin achieves its indispensable roles in animal development and neuronal survival. To address these questions, we are using both cell lines derived from human tissues as well as *Drosophila* as an animal model to take advantage of the power of these two complementary experimental systems.

Formation of aggregates by mutant Huntingtin is not only determined by polyQ length, but also influenced by other cellular and genetic factors, and their identification might help provide targets for therapeutic intervention for HD. To study aggregates, we have generated fruit fly lines carrying transgenes for human Huntingtin. Importantly, when expressed in different fly tissues such as in the eye, mutant Huntingtin protein form aggregates in a polyQ-length dependent manner whereas wildtype Huntingtin does not, demonstrating the feasibility of using this simple invertebrate system to model aggregates formation by mutant Huntingtin (Figure 5). To see which gene might regulate this aggregation process in a cell, we have further established a cell-based quantitative assay that allows automated measurement of aggregates. Using this assay, we have carried out a genome-wide screen by systematically knocking down the expression of every known gene in the fly genome using RNA interference (RNAi) and examining their effects on aggregate formation by mutant Huntingtin protein. From this large-scale screen, we have identified a group of genes that can increase or reduce aggregate formation. Functionally, these genes are involved in diverse cellular processes such as protein folding, trafficking and signaling. Their identification allows us to systematically tease out the molecular networks governing aggregate formation and potential neuronal toxicity.

Alteration of normal cellular functions of Huntingtin has been suspected to play a role in HD pathogenesis, however there is uncertainty as to how Huntingtin normally operates in a cell. Notably, no Huntingtin-like gene has been found in yeast or plants, but a single Huntingtin homolog (*dhtt*) exists in *Drosophila*, providing a unique opportunity to characterize Huntingtin in this powerful model organism. We have generated the first reported deletional mutant for this Huntingtin homolog. Interestingly, our studies suggest that *fly* Huntingtin is important for maintaining the mobility and long-term survival of adult animals. Loss of *dhtt* affects the complexity of axonal terminus, the site of cell-cell communication between neurons (Figure 6). Taking advantage of abundant tools in this model organism, we are focusing on dissecting out the normal functions of this enigmatic protein.

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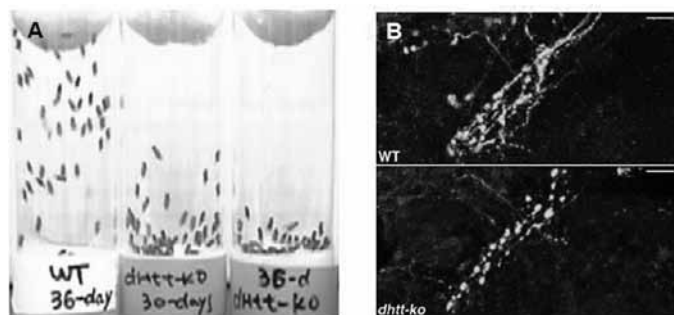


Figure 6.

(A) *Huntingtin* is required for the long-term mobility of adult flies. In this simple climbing assay, when adult flies contained in a vial are tapped down, they show robust negative geotaxis response by quickly climbing to the top of the vial, while flies mutated for *Huntingtin* homolog (*dhtt-ko*) show an accelerated decline of mobility as they age. In this movie clip, most normal flies (WT in the left vial, 36-day-old) already climb halfway to the top, while *dhtt-ko* mutant flies (30-day-old in the middle vial and 36-day-old in the right vial) mostly stay at the bottom of the containers.

(B) Images of axonal termini structure projected from a fluorescent-labeled neuron in an adult fly brain. Notice the reduced complexity of axonal termini in the *dhtt-ko* mutant (the bottom) as compared to normal control (top).

In summary, currently there are no effective prevention and treatment methods available for HD as well as most of the other brain degenerative disorders. Recent studies have demonstrated that these human brain diseases can be effectively modeled and studied in various experimental systems, including the invertebrate fruit fly. Knowledge learned from studying HD in this insect model could help shed light on tackling other multifactorial neurodegenerative illnesses. A better understanding of the molecular mechanisms underlying these devastating brain diseases might facilitate developing targeted and effective therapeutic approaches to help defeat their pressing threat to the well-being of our society.

#### About the Author

Dr. Sheng Zhang is an Assistant Professor in the Brown Foundation Institute of Molecular Medicine and the Department of Neurobiology and Anatomy at the University of Texas Medical School at Houston. He received his Ph. D. training from Yale University School of Medicine and completed his postdoctoral studies at Harvard Medical School. He joined the UT-HEALTH in 2008. His research focuses on pathogenic mechanisms of human brain degenerative diseases. His laboratory uses both mammalian systems and a simple genetic model *Drosophila melanogaster* (the fruit fly) to study the regulation of protein aggregation (i.e., abnormal protein deposits or plaques) as well as the cellular functions of the genes associated with *Huntingtin*'s and *Parkinson's* disorders.

sciousness? Neuroscientists are taking multiple approaches to study this problem. One common outcome of these studies is elucidation of the concept that neurons form extensive networks and electrical activity of these networks underlies the overall information processing capacity of the brain. Scientists are finding that multiple neuronal circuits exist simultaneously and coordinated activity of these circuits is required for the healthy functioning of the brain. Furthermore, when these networks go awry, the specter of neuropsychiatric disease rears its ugly head.

Neuronal networks are not ethereal entities. Rather, they consist of individual neurons forming physical connections called synapse with other neurons. The electrical activity of one neuron drives the activity of the other neurons connected to it. The principles of synapse development are geared to ensure optimal connectivity between neurons, and maintain electrical activity at a healthy level – neither too much nor too little, but just right. You may wonder how we study this process at the scale of a human brain? The short answer is that we don't! Instead of dealing with the grand complexities of the human brain (100 billion neurons and over 100 trillion synapses), scientists have chosen simple model organisms such as the fruit fly, *Drosophila melanogaster*, to study the development of synapses. Let me explain the utility of this approach. The fly brain has approximately a million times fewer neurons than the human brain. Despite this obvious "limitation", genetic factors that govern the development of each synapse and cues that drive network formation are remarkably well conserved between flies and humans. Therefore, what we learn from flies may be applicable to humans! This is not to say that flies (or any other model organism for that matter) are little people, but it is important to remember that biological patterns seen in humans are often also found in simpler organisms, albeit at a significantly smaller scale. Owing to this evolutionary truism, the overarching goal of my lab is to identify genes that direct synapse development and function in the fruit fly. So far, our approach has been to generate fly "knockout" lines missing genes whose human counterparts are associated with human neurologic disease, or ones that are highly enriched in the fly nervous system. Once we generate the mutant lines, we are able to evaluate the development and function of synapses in the mutant nervous system using well-established genetic, molecular, cell-biological, and electrophysiological tools. Indeed, it is no exaggeration to say that the tools available to study development of the nervous system in flies are truly exemplary!

Our recent studies have allowed us to identify key synaptic alterations in a *Drosophila* model of a human lysosomal storage disease called mucopolipidosis type IV (MLIV). MLIV is an early onset neurodegenerative disease that leads to severe psychomotor retardation in affected



children. One of the most debilitating outcomes of MLIV is the severe mental retardation and cognitive deficits that afflicts the patients. Sadly, the mechanistic basis of these outcomes is largely unknown. Using a *Drosophila* MLIV model I generated as a post-doctoral fellow at Johns Hopkins, my team at UT-Houston has found that in flies carrying mutations in the homolog of the gene disrupted in MLIV, synaptic growth and function at glutamatergic synapses is severely compromised. Furthermore, our studies raise the intriguing possibility that MLIV and perhaps other lysosomal storage diseases are characterized by alterations in mitogen activated protein kinase (MAPK) signaling pathway in axons. Based on our findings, we predict that owing to diminished MAPK signaling, major axonal tracts such as those of the corpus callosum may not develop adequately in MLIV patients resulting in psychomotor retardation. The future of this project involves using flies to further characterize the synaptic alterations and translate our findings to a mouse model of MLIV. We also hope that pharmacological modification of the MAPK signaling pathway may be tested for alleviating the clinical outcomes of MLIV.

In addition, we have identified other genes whose protein products are involved in the development and function of glutamatergic synapses in flies. These include an axonal endoplasmic reticulum (ER) resident cation channel responsible for releasing stored Ca<sup>2+</sup> to maintain synaptic growth and resting Ca<sup>2+</sup> levels at glutamatergic synapses. Interestingly, our research suggests that alterations in axonal ER Ca<sup>2+</sup> may also be occurring in certain familial forms of the human motor neuron disease, amyotrophic lateral sclerosis (ALS). Supporting this proposal, the absence of the Ca<sup>2+</sup> channel we are studying lead to axonal and synaptic changes that are very similar to those occurring in a *Drosophila* model of ALS. Moreover, when the mutant protein synthesized in patients with an inherited form of ALS is expressed in *Drosophila* motor neurons, it appears to be exerting its toxic effects via this Ca<sup>2+</sup> channel. Owing to the stellar pharmacological tractability of Ca<sup>2+</sup> channels, our research may open new avenues of therapeutic interventions for tackling ALS.

Another gene we have identified encodes a protein that is over 100-fold enriched in the fly nervous system compared to other tissues. This protein is likely a novel transsynaptic molecule responsible for keeping the presynaptic and postsynaptic membranes in close apposition. Excitingly, this gene is conserved in vertebrates and we hope that future studies in rodent models will find that this gene encodes a protein essential for regulating key functions of the nervous system.

Ultimately, the goal of my lab is to utilize a collaborative effort between several disciplines to inch forward in our quest to understand the regulation of neuronal interconnectedness. Without this knowledge, we can neither

treat the plethora of neuropsychiatric diseases affecting humans nor can we hope to get to the heart of the existentialist questions that have intrigued us for millennia.

#### About the Author

*Dr. Kartik Venkatachalam received his Ph.D. in the laboratory of Dr. Donald Gill at the University of Maryland, School of Medicine. Subsequently, he joined the laboratory of Dr. Craig Montell, at the Johns Hopkins University School of Medicine as a post-doctoral fellow. At Hopkins, Dr. Venkatachalam developed a fly model of a childhood onset neurodegenerative disease. He joined UT-Houston as an Assistant Professor in the department of Integrative Biology and Pharmacology in 2010. Here, Dr. Venkatachalam is crafting a research program evaluating the role of synaptic physiology in human health and disease. For more information, visit: [www.utflylab.com](http://www.utflylab.com)*

#### CONTINUED FROM PAGE 3; AWARDS

**Ponnada Narayana**, Professor, Department of Diagnostic and Interventional Imaging, was named a 2012 fellow of the International Society for Magnetic Resonance in Medicine (ISMRM) in honor of his contributions to the field of MR imaging, and honored at the ISMRM annual meeting in May in Melbourne, Australia.

**Hope Northrup**, Professor, Department of Pediatrics, was awarded the 2012 Wise Woman HER Award by *Houston Woman Magazine* in July, which recognizes a teacher or mentor who has provided guidance that has had a significant impact on the outcome of others' lives.

**Henry W. Strobel**, Associate Dean for Faculty Affairs and Alumni Relations, received the prestigious Honorary Professorship Award from Capital Medical University, Beijing, China. This is the highest honor is given to professors who have offered great contributions to its university in areas of academics, faculty training, and collaboration.

**Anthony A. Wright**, Professor, Department of Neurobiology and Anatomy, received the Comparative Cognition Society (CCS) Research Award at the Spring 2012 meeting, where he delivered the "Master" lecture. In addition, a special issue of *Behavioural Processes* will be soon feature contributions and articles by Dr. Wright and his collaborators and colleagues.

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The NRC is able to host events free to the public because of the continued support and generosity of individuals in the community.

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# 19th Annual Neuroscience Poster Session

The UTHealth Neuroscience Research Center was pleased to co-host the 19th Annual Neuroscience Poster Session with Baylor College of Medicine (BCM) Department of Neuroscience and Rice University Department of Psychology. The event, which was our largest poster session to date, was held at the new Denton A. Cooley, MD and Ralph C. Cooley, DDS University Life Center on Saturday, December 1, 2012. Seventy-five posters were presented from faculty, research scientists, graduate and medical students from all three institutions.

## Graduate Student Awards

UTHealth 1st place award: The Dee S. and Patricia Osborne Endowed Scholarship in the Neurosciences  
Brittany Parker

Baylor College of Medicine 1st place award:  
Loredana Stoica

Rice University 1st place award: Gertrude Maurin Cognitive Neuroscience Research Award

Debshila Basu Mallick

Overall 2nd place prizes:

Josephine De Asis-Cruz, BCM

2nd place Erika Perez, BCM

Overall 3rd place prizes:

3rd place Alyse Thomas, BCM

3rd place Mingbo Cai, BCM

## Postdoctoral Fellow Awards

1st place David MacLean, UTHealth

2nd place Christopher Whitaker, UTHealth

3rd place Bryan Hansen, UTHealth



Jack Byrne poses with 1st place postdoctoral fellow poster winner, David MacLean (UTHealth).



Jack Byrne, Chair of the Department of Neurobiology and Anatomy, UTHealth, and Director of the Neuroscience Research Center, poses with UTHealth 1st place graduate student winner and recipient of the Dee S. and Patricia Osborne Endowed Scholarship in the Neurosciences, Brittany Parker.



Jim Dannemiller, Chair of the Department of Psychology, Rice University, poses with Rice University first place graduate student winner and recipient of the Gertrude Maurin Cognitive Neuroscience Research Award, Debshila Basu Mallick.



Dora Angelaki, Chair of the Department of Neuroscience, Baylor College of Medicine, poses with BCM first place graduate student winner, Loredana Stoica.



Group shot of judges from all three participating institutions.



Group shot of poster presenters from all three participating institutions.

# in the Spotlight



For a second year, the NRC has welcomed high school students from the Worthing Rice Apprentice Program (WRAP) to tour the laboratory of Dr. Jack Byrne. This program is coordinated by Dr. Steve Cox (Rice University) and allows local high school students to study neuroscience with Rice students and faculty.



July 12, 2012  
A group of Neuroscience Program graduate students discuss neuroscience research, getting into graduate school, and career paths with highly motivated high school students through the National Youth Leadership Forum program.



October 15, 2012  
NRC Reception at the annual meeting of the Society for Neuroscience, New Orleans, LA.

## upcoming Events

### 18th Annual Public Forum

**"Concussions: Advances in Prevention, Diagnosis and Treatment"**

**Saturday, February 23, 2013  
10:30 am to Noon**

UTHealth Cooley University Life Center,  
7400 Cambridge St., Houston, TX

### BRAIN NIGHT



### FOR KIDS 2013

**Thursday, March 14, 2013  
6:00 - 8:00 pm, The Health Museum  
151 Hermann Drive, Houston, Texas**



## Keep in Touch!

Website: <http://nba.uth.tmc.edu/nrc>

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## Questions? Comments?

Contact us at 713-500-5538

or E-mail: [nba-nrc@uth.tmc.edu](mailto:nba-nrc@uth.tmc.edu)

Check out our Neurofax calendar of neuroscience events on-line! The Neurofax includes seminars, grand rounds, research colloquia, symposia, and local or national conferences that are sponsored by UTHealth, the Texas Medical Center, and Houston area universities and research institutions. To submit your event to this calendar, please send an email to [nba-nrc@uth.tmc.edu](mailto:nba-nrc@uth.tmc.edu) and include Event Name, Event Contact, Date, Time and Location.

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