# Joshua M. Shulman, M.D., Ph.D.


- **Assistant Professor of Neurology and Molecular & Human Genetics**
- **Investigator, Jan and Dan Duncan Neurological Research Institute, Texas Children's Hospital**
- **Principal Investigator, Laboratory for Integrative Functional Genomics**

### Clinical Service Area

Neurology

### Specialty

Neurogenetics
Parkinson's Disease
Movement Disorders

### Clinic Appointments

713-798-7438

### Consult

713-798-7438

### Medical School

M.D., Harvard Medical School & M.I.T. Health Sciences and Technology, Boston, Mass.

### Graduate School

Ph.D., University of Cambridge, United Kingdom

### Internship

Internal Medicine, Massachusetts General Hospital, Boston, Mass.

### Residency

Neurology, Brigham and Women's Hospital & Massachusetts General Hospital, Boston, Mass.

### Clinical Fellowship

Movement and Memory Disorders, Brigham and Women's Hospital & Massachusetts General Hospital, Boston, Mass.

### Post-Doctoral Research Fellowship

Neurogenetics, Brigham and Women's Hospital & Broad Institute of Harvard/M.I.T., Boston, Mass.

### Clinic Location

Baylor Neurology
Smith Tower
6550 Fannin, Suite 1801
Houston, Texas 77030

## Clinical Interests

Parkinson's disease and related movement disorders

## Research Areas

- Functional genomics of Alzheimer's disease and Parkinson's disease
- Integrative genetic analyses in humans and *Drosophila*

## Research Interests

## Integrative Functional Genomics in Neurodegenerative Disease

Recent advances have made the discovery of genetic susceptibility loci for complex human phenotypes a reality, including nervous system disorders. The critical next step will be to definitively identify the responsible genes and understand their functions in both health and disease. Our research integrates genetic investigation in human subjects and model organisms, with the goal of understanding brain function and aging, and improving the treatment of neurologic disease. We focus on Alzheimer's disease and Parkinson's disease, two incurable neurodegenerative disorders and experimental paradigms for the age-dependent failure of brain cognitive and motor control in humans.

### Human Genetics

The clinical manifestation of neurodegenerative disease is the culmination of a multi-tiered pathogenic cascade that evolves over decades—understanding how genetic variants impact this causal chain is essential. Although 2% of the population over age 65 are clinically diagnosed with Parkinson's disease, the defining pathology of disease (alpha-synuclein Lewy bodies) is discovered in 20% of brains from population-based autopsy studies. We are therefore investigating the impact of genomic variation on directly measured Lewy pathology, neuronal loss in the midbrain substantia nigra, and progressive motor impairment, leveraging human subject cohorts with detailed clinical and pathological data. We also participate in collaborative studies for the functional genetic dissection of Alzheimer's disease, focusing on the responsible neuropathology, amyloid neuritic plaques and Tau neurofibrillary tangles.

### *Drosophila* Genetics

Despite the promise of current human genetic methods, such as genome-wide association studies, they often fail to identify disease susceptibility genes with certainty, instead highlighting broad genomic regions. We are taking advantage of the rapid and powerful genetics available in the fruit fly*Drosophila melanogaster* in order to accelerate the validation of responsible genes and an understanding of their functions in disease pathogenesis. Expression of human amyloid-beta, Tau, or alpha-synuclein proteins in the fly nervous system recapitulates many core features of Alzheimer's disease and Parkinson's disease pathogenesis. We are testing candidate human susceptibility genes for functional genetic interactions in these fly models of neurodegeneration. Implicated molecular pathways are probed in greater depth, using both*Drosophila* and human genetic approaches. Our strategy has recently identified cell adhesion converging on the cytoskeleton as likely important for Tau-mediated neurodegeneration and Alzheimer's disease susceptibility, and we are now following up these insights to elucidate the detailed mechanisms.

## Contact Information

Joshua M. Shulman, M.D., Ph.D.
Jan and Dan Duncan Neurological Research Institute
1250 Moursund St., Suite N.1150
Houston, Texas 77030

Tel: 832-824-8806
Fax: 832-825-1249
Email: Joshua.Shulman@bcm.edu

## Journal Publications

1. Buchman AS, Yu L, Wilson RS, Shulman JM, Boyle PA, Bennett DA. Harm avoidance is associated with progression of parkinsonism in community-dwelling older adults: a prospective cohort study. BMC

Geriatr. 2014;14(1):54. [View journal article]

2. Haelterman NA, Yoon WH, Sandoval H, Jaiswal M, Shulman JM, Bellen HJ. A mitocentric view of Parkinson's disease. Annu Rev Neurosci. 2014;37:137-59. [View journal article]
3. Sherva R, Tripodis Y, Bennett DA, Chibnik LB, Crane PK, de Jager PL, et al. Genome-wide association study of the rate of cognitive decline in Alzheimer's disease. Alzheimers Dement. 2014;10(1):45-52. [View journal article]
4. Shulman JM, Imboywa S, Giagtzoglou N, Powers MP, Hu Y, Devenport D, et al. Functional screening in Drosophila identifies Alzheimer's disease susceptibility genes and implicates Tau-mediated mechanisms. Hum Mol Genet. 2014;23(4):870-7. [View journal article]
5. Shulman JM, Yu L, Buchman AS, Evans DA, Schneider JA, Bennett DA, et al. Association of Parkinson disease risk Loci with mild parkinsonian signs in older persons. JAMA Neurol. 2014;71(4):429-35. [View journal article]
6. Cruchaga C, Kauwe JS, Harari O, Jin SC, Cai Y, Karch CM, et al. GWAS of cerebrospinal fluid tau levels identifies risk variants for Alzheimer's disease. Neuron. 2013;78(2):256-68. [View journal article]
7. Shulman JM, Chen K, Keenan BT, Chibnik LB, Fleisher A, Thiyyagura P, et al. Genetic susceptibility for Alzheimer disease neuritic plaque pathology. JAMA Neurol. 2013;70(9):1150-7. [View journal article]
8. Shulman JM. Structural variation and the expanding genomic architecture of Parkinson disease. JAMA Neurol. 2013;70(11):1355-6. [View journal article]
9. Biffi A, Shulman JM, Jagiella JM, Cortellini L, Ayres AM, Schwab K, et al. Genetic variation at CR1 increases risk of cerebral amyloid angiopathy. Neurology. 2012;78(5):334-41. [View journal article]
10. Bis JC, DeCarli C, Smith AV, van der Lijn F, Crivello F, Fornage M, et al. Common variants at 12q14 and 12q24 are associated with hippocampal volume. Nat Genet. 2012;44(5):545-51. [View journal article]
11. Buchman AS, Shulman JM, Nag S, Leurgans SE, Arnold SE, Morris MC, et al. Nigral pathology and parkinsonian signs in elders without Parkinson disease. Ann Neurol. 2012;71(2):258-66. [View journal article]
12. De Jager PL, Shulman JM, Chibnik LB, Keenan BT, Raj T, Wilson RS, et al. A genome-wide scan for common variants affecting the rate of age-related cognitive decline. Neurobiol Aging. 2012;33(5):1017 e1-15. [View journal article]
13. Keenan BT, Shulman JM, Chibnik LB, Raj T, Tran D, Sabuncu MR, et al. A coding variant in CR1 interacts with APOE-epsilon4 to influence cognitive decline. Hum Mol Genet. 2012;21(10):2377-88. [View journal article]
14. Raj T, Shulman JM, Keenan BT, Chibnik LB, Evans DA, Bennett DA, et al. Alzheimer disease susceptibility loci: evidence for a protein network under natural selection. Am J Hum Genet. 2012;90(4):720-6. [View journal article]
15. Yu L, Shulman JM, Chibnik L, Leurgans S, Schneider JA, De Jager PL, et al. The CETP I405V polymorphism is associated with an increased risk of Alzheimer's disease. Aging Cell. 2012;11(2):228-33. [View journal article]
16. Chibnik LB, Shulman JM, Leurgans SE, Schneider JA, Wilson RS, Tran D, et al. CR1 is associated with amyloid plaque burden and age-related cognitive decline. Ann Neurol. 2011;69(3):560-9. [View journal article]
17. Shulman JM, Chipendo P, Chibnik LB, Aubin C, Tran D, Keenan BT, et al. Functional screening of Alzheimer pathology genome-wide association signals in Drosophila. Am J Hum Genet. 2011;88(2):232-8. [View journal article]
18. Shulman JM, De Jager PL, Feany MB. Parkinson's disease: genetics and pathogenesis. Annu Rev Pathol. 2011;6:193-222. [View journal article]
19. Treusch S, Hamamichi S, Goodman JL, Matlack KE, Chung CY, Baru V, et al. Functional links between Abeta toxicity, endocytic trafficking, and Alzheimer's disease risk factors in yeast. Science. 2011;334(6060):1241-5. [View journal article]
20. Corneveaux JJ, Myers AJ, Allen AN, Pruzin JJ, Ramirez M, Engel A, et al. Association of CR1, CLU and PICALM with Alzheimer's disease in a cohort of clinically characterized and neuropathologically verified individuals. Hum Mol Genet. 2010;19(16):3295-301. [View journal article]
21. Shulman JM, Chibnik LB, Aubin C, Schneider JA, Bennett DA, De Jager PL. Intermediate phenotypes identify divergent pathways to Alzheimer's disease. PLoS One. 2010;5(6):e11244. [View journal article]
22. Shulman JM. Incidence and risk for dementia in Parkinson disease. Journal Watch: Neurology. 2010;12(4):28.
23. Xia Z, Chibnik LB, Glanz BI, Liguori M, Shulman JM, Tran D, et al. A putative Alzheimer's disease risk

allele in PCK1 influences brain atrophy in multiple sclerosis. PLoS One. 2010;5(11):e14169. [View journal article]

24. Shulman JM, De Jager PL. Evidence for a common pathway linking neurodegenerative diseases. Nat Genet. 2009;41(12):1261-2. [View journal article]
25. Alcalay RN, Shulman JM, Plotkin SR. Ramsay Hunt syndrome in a patient with metastatic lung cancer to brain. J Neurooncol. 2008;86(1):55-6. [View journal article]
26. Steinhilb ML, Dias-Santagata D, Mulkearns EE, Shulman JM, Biernat J, Mandelkow EM, et al. S/P and T/P phosphorylation is critical for tau neurotoxicity in Drosophila. J Neurosci Res. 2007;85(6):1271-8. [View journal article]
27. Khurana V, Lu Y, Steinhilb ML, Oldham S, Shulman JM, Feany MB. TOR-mediated cell-cycle activation causes neurodegeneration in a Drosophila tauopathy model. Curr Biol. 2006;16(3):230-41. [View journal article]
28. Shulman JM. Wing of fly, tail of rodent, scale of fish, and pinch of yeast: cooking up the ultimate animal model in movement disorders. Moving Along. 2005;7(1):1.
29. Shulman JM. Surgical lessons from Shakespeare. Curr Surg. 2004;61(1):96-7. [View journal article]
30. Doerflinger H, Benton R, Shulman JM, St Johnston D. The role of PAR-1 in regulating the polarised microtubule cytoskeleton in the Drosophila follicular epithelium. Development. 2003;130(17):3965-75. [View journal article]
31. Shulman JM, Feany MB. Genetic modifiers of tauopathy in Drosophila. Genetics. 2003;165(3):1233-42. [View journal article]
32. Shulman JM, Shulman LM, Weiner WJ, Feany MB. From fruit fly to bedside: translating lessons from Drosophila models of neurodegenerative disease. Curr Opin Neurol. 2003;16(4):443-9. [View journal article]
33. Tree DR, Shulman JM, Rousset R, Scott MP, Gubb D, Axelrod JD. Prickle mediates feedback amplification to generate asymmetric planar cell polarity signaling. Cell. 2002;109(3):371-81. [View journal article]
34. Huynh JR, Shulman JM, Benton R, St Johnston D. PAR-1 is required for the maintenance of oocyte fate in Drosophila. Development. 2001;128(7):1201-9. [View journal article]
35. Wittmann CW, Wszolek MF, Shulman JM, Salvaterra PM, Lewis J, Hutton M, et al. Tauopathy in Drosophila: neurodegeneration without neurofibrillary tangles. Science. 2001;293(5530):711-4. [View journal article]
36. Shulman JM, Benton R, St Johnston D. The Drosophila homolog of C. elegans PAR-1 organizes the oocyte cytoskeleton and directs oskar mRNA localization to the posterior pole. Cell. 2000;101(4):377-88. [View journal article]
37. Shulman JM, St Johnston D. Pattern formation in single cells. Trends Cell Biol. 1999;9(12):M60-4. [View journal article]
38. Axelrod JD, Miller JR, Shulman JM, Moon RT, Perrimon N. Differential recruitment of Dishevelled provides signaling specificity in the planar cell polarity and Wingless signaling pathways. Genes Dev. 1998;12(16):2610-22. [View journal article]
39. Shulman JM, Perrimon N, Axelrod JD. Frizzled signaling and the developmental control of cell polarity. Trends Genet. 1998;14(11):452-8. [View journal article]

## Poster and Platform Presentations

1. Shulman J, Yu L, Buchman A, Evans D, Schneider J, Bennett D, et al. Exploring the impact of Parkinson disease (PD) susceptibility genes in elders without PD. Neurology. 2013;80(Meeting Abstracts 1):S13.006. [Platform Presentation]
2. Shulman JM, Chen K, Keenan BT, Chibnik LB, Thiyyagura P, McCabe C, et al. Genetic susceptibility for amyloid pathology in Alzheimer's disease. Ann Neurol. 2012;72 Suppl 16:S51.
3. Shulman JM, Imboywa S, Diamond AE, Chipendo P, De Jager PL, Feany MB. Integrating human and fly genetics to understand Alzheimer's disease susceptibility. Ann Neurol. 2012;72 Suppl 16:S51.
4. Shulman JM. Genetic analyses of Parkinson's disease endophenotypes. Presented at the Parkinson Study Group (PSG), 26th Annual Symposium on Etiology, Pathogenesis, and Treatment of Parkinson Disease and Other Movement Disorders in Irving, Texas (May 11, 2012). [Platform Presentation]
5. Shulman JM, Chipendo PI, Chibnik LB, Keenan BT, Tran D, Huentelman MA, et al. Integrating genome-wide association and functional validation to understand susceptibility for Alzeheimer's

pathology. Ann Neurol. 2011;70 Suppl 15:S50-1. [Platform Presentation]

6. Shulman JM. What can endophenotypes teach us about Parkinson's disease? Presented at the Michael J. Fox Parkinson's Research Foundation, Genetic Epidemiology of Parkinson's Disease Consortium Meetiing in Evanston, Ill. (Sept. 18-21, 2011). [Oral Presentation]
7. Keenan B, Shulman J, Chibnik L, Corneveaux J, Allen A, Myers A, et al. A candidate causal variant in the CR1 locus. Alzheimers Dement. 2011;7(4 Suppl):S496-S7.
8. Raj T, Shulman J, Chibnik L, Keenan B, Stranger B, Evans D, et al. Alzheimer's disease susceptibility loci: Evidence for natural selection and altered gene expression. Alzheimers Dement. 2011;7(4 Suppl):S183.
9. Sherva R, Tripodis Y, Shulman J, Chibnik L, Crane P, Bennett D, et al. Genetic factors associated with the rate of cognitive decline in Alzheimer's disease. Alzheimers Dement. 2011;7(4 Suppl):S496.
10. Shulman J, Chibnik L, Keenan B, Destefano A, Leurgans S, Wilson R, et al. A genome-wide association scan for episodic memory decline in aging. Alzheimers Dement. 2011;7(4 Suppl):S195.
11. Shulman J, Chipendo P, Chibnik L, Keenan B, Tran D, Aubin C, et al. Integrating genome-wide association and functional validation to understand susceptibility for Alzheimer's pathology. Alzheimers Dement. 2011;7(4 Suppl):S497. [Platform Presentation]
12. Shulman JM, Chibnik LB, Leurgans SE, Wilson RS, Tran D, Keenan BT, et al. A genome-wide association scan for episodic memory decline in aging. Neurology. 2011;76(Suppl 4):A1-2. [Platform Presentation]
13. Shulman JM, Keenan BT, Chibnik LB, Raj T, Tran D, Aubin C, et al. Functional fine mapping of the CR1 locus identifies a causal variant for Alzheimer's disease susceptibility. Neurology. 2011;76(Suppl 4):A642. [Platform Presentation]
14. Shulman JM. Enhancing power for gene discovery in Alzheimer's disease: Intermediate phenotypes and functional validation in drosophila. Presented at the Keystone Symposium, Symposium on Neurodegenerative Diseases in Taos, N.M. (Feb. 21-26, 2011). [Platform Presentation]
15. Shulman JM. Genomics of cognitive decline and neuropathology. Presented at the Rush University, ROS/MAP Investigator Meeting in Chicago, Ill.(2011). [Oral Presentation]
16. Shulman JM, Chipendo1 P, Aubin C, Kramer P, Schneider JA, Bennett DA, et al. Enhancing power for gene discovery in Alzheimer's disease: Intermediate phenotypes and functional validation in drosophila. Presented at the American Society of Human Genetics (ASHG), 60th Annual Meeting in Washington, DC (Nov. 2-6, 2010). [Platform Presentation]
17. De Jager P, Chibnik L, Aggarwal N, Shulman J, Schneider J, Evans D, et al. Relation of the Alzheimer's disease susceptibility allele at the CR1 locus to cognitive decline and Alzheimer's disease neuropathology in older persons. Neurology. 2010;74(9 Suppl 2):A97. [Platform Presentation]
18. Shulman JM, Aubin C, Tran D, Kramer P, Feany MB, Bennett D, et al. Enhancing power for gene discovery in Alzheimer's disease: Intermediate phenotypes and functional validation in drosophila. Neurology. 2010;74(9 Suppl 2):A500. [Platform Presentation]
19. Xia Z, Chibnik LB, Shulman JM, Aubin C, Tran D, Glanz BI, et al. Alzheimer's disease risk alleles in PCDH11X and SORL1 are associated with the rate of cognitive decline in subjects with multiple sclerosis. Neurology. 2010;74(9 Suppl 2):A313-4. [Platform Presentation]
20. Shulman JM. Genome-wide association scans for cognitive decline. Presented at the Rush University, CHAP Investigator Meeting in Chicago, Ill. (2010). [Oral Presentation]
21. Shulman JM. A role for PAR-1 in oocyte determination. Presented at the Genetics Society of America (GSA), 41st Annual Drosophila Research Conference in Pittsburgh, Penn. (March 22-26, 2000). [Platform Presentation]
22. Shulman JM. A drosophila homologue of c. elegans PAR-1. Presented at the British Society for Developmental Biology (BSDB), BSCB/BSDB Joint Spring Meeting in Manchester, England (April 13-16, 1999). [Platform Presentation]
23. Shulman JM. A drosophila homologue of c. elegans PAR-1. Presented at the Genetics Society of America (GSA), 40th Annual Drosophila Research Conference in Bellevue, Wash. (March 24-28, 1999). [Platform Presentation]
24. Shulman JM. Subcellular relocalization of dishevelled mediates polarity signaling. Presented at the Genetics Society of America (GSA), 39th Annual Drosophila Research Conference in Washington, DC (March 25-29, 1998). [Platform Presentation]
25. Shulman JM. Dishevelled is a multifunctional signal transducer. Presented at the Genetics Society of America (GSA), 37th Annual Drosophila Research Conference in San Diego, Calif. (April 27 - May 1, 1996). [Platform Presentation]