## BIOGRAPHICAL SKETCH

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NAME: Dawn Hsiao-Wei Loh

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Associate Project Scientist

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| University of Edinburgh, United Kingdom | B.Sc. | 06/1998 | Genetics |
| Medical Research Center for Human Genetics, Edinburgh, United Kingdom | Ph.D. | 03/2004 | Molecular Genetics |
| University of California - Los Angeles | Postdoctoral | 06/2010 | Neuroscience |

### A. Personal Statement

Disruptions in the circadian system are commonly associated with aging and disease, including neurodevelopmental and neurodegenerative disorders. These circadian disruptions have a major impact on the quality of life of people throughout the world and are among the first symptoms seen in diseases of the nervous system. Broadly speaking, I am interested in discovering the mechanisms that underlie these disturbances and, critically, in testing the hypothesis that manipulations of the sleep/wake cycle can alter the trajectory of the symptoms and pathology of neuronal diseases. As the co-PI on a university-funded grant, I began the characterization of circadian rhythm disruption in the *Cntnap2* mouse model of autism spectrum disorder (ASD). I led a multi-lab study on sleep and circadian rhythm disruption in the *Mecp2*$^{loxP}$ mouse model of Rett syndrome, demonstrating severe disruption of circadian rhythms of sleep and activity in the model. With my colleagues, I characterized similar disruptions to the circadian system in mouse models of Huntington's disease (HD), a neurodegenerative disorder. These mouse models of disease recapitulate the sleep/wake cycle dysfunction common to patients of neurological disorders. The next phase of this program of work involves treatment of the circadian dysfunction using timed food access, improved lighting environments, and pharmacological agents. The value of these circadian treatments will be determined by examining their impact on behavioral symptoms and physiological function in mouse models of ASD, RTT, and HD. My preclinical research reveals strong links between circadian disruption and neuropsychiatric disease that needs to be studied in the patient populations. To achieve this, I am collaborating with a Huntington's disease clinic at UCLA to characterize sleep/wake and circadian disruption in patients with pre-manifest HD. A critical part of this study is to develop an at-home monitoring assay for sleep and circadian disruption as a biomarker. Our ability to manage and ameliorate the effects of poor sleep are contingent on having accessible tools to record the sleep-wake cycle of patients in their daily lives.

### B. Positions and Honors

**Positions and Employment**

2003-2005 Research Assistant, Division of Neuroscience, University of Edinburgh
2005-2010 Postdoctoral Fellow, Department of Psychiatry and Biobehavioral Sciences, University of California – Los Angeles
2010-2015 Research Associate, Department of Psychiatry and Biobehavioral Sciences, University of California – Los Angeles

2015- Associate Project Scientist, Department of Psychiatry and Biobehavioral Sciences, University of California – Los Angeles

**Other Experience and Professional Memberships**

2008-present Member, Society for Research on Biological Rhythms
2009-present Member, Society for Neuroscience
2011-present Member, European Biological Rhythms Society
2013-present Ad hoc grant reviewer, UCLA Undergraduate Research Fellowship Program

**Honors**

2015 Huntington's Disease Society of America Fellowship
2013 UCLA Friends of the Semel Institute Award

**C. Contribution to Science**

1. Temporal patterns of sleep and wake, along with other aspects of behavior and physiology, are governed by the circadian timing system. In mammals, the primary circadian pacemaker is a pair of nuclei located in the hypothalamus: the suprachiasmatic nuclei (SCN). The SCN acts as a major integrator of environmental input, allowing mammals to adapt to changing circumstances, and regulates other brain regions and peripheral organs using local neural or global hormonal output signals, which has been the focus of my work to date. A particular strength of this work has been the integration of the SCN pacemaker and peripheral circadian oscillators, examining the impact of a weakened SCN on a range of behavioral and physiological outputs. My postdoctoral research has addressed the importance of robust cellular synchrony within the neurons of the SCN (Kudo et al. 2011), how perturbation of synchrony has downstream effects on the daily rhythms in hormones and gene expression in the peripheral organs (Loh et al. 2008 and 2011), cognition (Chaudhury, Loh et al. 2008), cardiovascular function (Schroeder et al. 2011), and the female reproductive system (Loh et al. 2014). My expertise in characterization of circadian activity, sleep, behavior, gene expression, and hormones were key to the studies.

    a. Loh DH, Kuljis DA, Azuma L, Wu Y, Truong D, Wang HB, Colwell CS (2014) Disrupted reproduction, estrous cycle, and circadian rhythms in female mice deficient in vasoactive intestinal peptide. J Biol Rhythms, 29(5):355-69. PMID: 25252712. PMCID: PMC4353614.
    b. Loh DH, Dragich JM, Kudo T, Schroeder AM, Nakamura TJ, Waschek JA, Block GD, Colwell CS (2011) Effects of vasoactive intestinal peptide genotype on circadian gene expression in the suprachiasmatic nucleus and peripheral organs. J Biol Rhythms, 26(3):200-9. PMID: 21628547. PMCID: PMC3942163.
    c. Kudo T*****, Loh DH*****, Kuljis D, Constance C, Colwell CS (2011) Fast delayed rectifier potassium current: critical for input and output of the circadian system. J Neurosci., 31(8):2746-55. PMID: 21414897. PMCID: PMC4344835. *Joint 1st author.
    d. Loh DH, Abad C, Colwell CS, Waschek JA (2008) Vasoactive intestinal peptide is critical for circadian regulation of glucocorticoids. Neuroendocrinology, 88(4):246-55. PMID: 18562786. PMCID: PMC2590621. (Recommended by the Faculty of 1000.)

2. In parallel, I have characterized sleep and circadian disruption in the behavior of mouse models of neurodevelopmental disorders (Li et al. 2015) and neurodegenerative disorders (Kudo et al. 2011; Kudo et al. 2011; and Loh et al. 2013). The sleep and circadian disruption exhibited by these genetic models of disease reflect the sleep disturbances reported by patients with Rett syndrome, Huntington's disease (HD), and Parkinson's disease. This supports the face validity of using these models for pre-clinical tests of therapies that target the sleep/wake cycle. The main thrust of my current work examines the impact of circadian disruption, and correspondingly, circadian treatment on disease symptoms. I have determined a positive impact of circadian intervention on the disease progression of motor dysfunction on two independent lines of HD mutant mice (manuscript in preparation). Specifically, the treatments use timed feeding schedules to re-align activity to the appropriate time of day, resulting in boosted circadian rhythms and improved performance on the rota rod and beam traversal tests compared to untreated controls.

a. Li Q*, Loh DH*, Kudo T, Truong D, Derakhshesh M, Kaswan ZM, Ghiani CA, Tsoa R, Cheng Y, Sun YE, Colwell CS.(2015) Circadian rhythm disruption in a mouse model of Rett syndrome circadian disruption in RTT. Neurobiol Dis., 77:155-64. *Equal contribution. PMID: 25779967.
b. Loh DH, Kudo T, Truong D, Wu Y, Colwell CS (2013) The Q175 mouse model of Huntington's disease shows gene dosage- and age-related decline in circadian rhythms of activity and sleep. PLoS One, 8(7):e69993. PMID: 23936129. PMCID: PMC3728350.
c. Kudo T, Loh DH, Tahara Y, Truong D, Hernández-Echeagaray E, Colwell CS (2014) Circadian dysfunction in response to in vivo treatment with the mitochondrial toxin 3-nitropropionic acid. ASN Neuro.6(1):e00133. PMID: 24328694. PMCID: PMC3891360.
d. Schroeder AM, Loh DH, Jordan MC, Roos KP, Colwell CS (2011) Baroreceptor reflex dysfunction in the BACHD mouse model of Huntington's disease. PLoS Curr. 3:RRN1266. PMID: 22069044. PMCID: PMC3208373.
e. Kudo T, Loh DH, Truong D, Wu Y, Colwell CS (2011) Circadian dysfunction in a mouse model of Parkinson's disease. Exp Neurol., 66-75. PMID: 21864527.
f. Kudo T, Schroeder A, Loh DH, Kuljis D, Jordan MC, Roos KP, Colwell CS (2011) Dysfunctions in circadian behavior and physiology in mouse models of Huntington's disease. Exp Neurol., 228(1):80-90. PMID: 21184755. PMCID: PMC4346330.

3. My work on mouse mutants with disrupted circadian rhythms highlighted how desynchrony or misalignment of the circadian oscillators in the brain and periphery has deleterious effects on cognitive and physiological processes. Cognitive performance is dependent on time of day, and the neural circuits involved in learning and memory also exhibit circadian rhythms in gene expression and synaptic plasticity. Testing of this hypothesis led to a study on misaligning the circadian oscillators by applying experimental jet lag to mice, which severely affected memory (Loh et al. 2010). Even a single jet lag event had marked effects on memory, which has profound implications for those suffering from chronic circadian disruption. Additionally, chronic circadian disruption is a growing public health problem, with many people living in an environment where their circadian system is challenged by inappropriate meal- or work-times. To test this, I have recently completed a study examining the impact of inappropriate meal times on cognition (Loh et al. 2015). In it, I demonstrate the circadian oscillator in the hippocampus is affected by the timing of food availability, and misaligns it from the SCN. This chronic circadian misalignment causes reduced hippocampal long term potentiation and CREB expression. Importantly this mis-timed feeding resulted in dramatic deficits in hippocampal-dependent learning and memory. My findings suggest that circadian misalignment has far-reaching effects on hippocampal physiology and highlights the importance of circadian regulation on cognition.

    a. Loh DH, Jami SA, Flores RE, Truong D, Ghiani CA, O'Dell TJ, Colwell CS (2015) Misaligned feeding impairs memories. eLife. 10.7554/eLife.09460.
    b. Loh DH, Navarro J, Hagopian A, Wang LM, Deboer T, Colwell CS (2010) Rapid changes in the light/dark cycle disrupt memory of conditioned fear in mice. PLoS One., 5(9): e12546. PMID: 20824058. PMCID: PMC2932734.
    c. Gerstner JR, Lyons LC, Wright KP Jr, Loh DH, Rawashdeh O, Eckel-Mahan KL, Roman GW (2009) Cycling behavior and memory formation. J Neurosci., 29(41):12824-30. PMID: 19828795. PMCID: PMC4077269.
    d. Chaudhury D, Loh DH, Dragich JM, Hagopian A, Colwell CS (2008) Select cognitive deficits in vasoactive intestinal peptide deficient mice. BMC Neurosci., 9:63. PMID: 18616823. PMCID: PMC2474849.

**Complete List of Published Work in MyBibliography:**
http://www.ncbi.nlm.nih.gov/sites/myncbi/1rCljOD997lkb/bibliography/47472494/public/?sort=date&direction=descending