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Genome-scale study identifies hundreds of potential drug targets for Huntington's disease

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Scientists searching for ways to develop treatments for Huntington's disease (HD) just got a roadmap that could dramatically speed their discovery process. Researchers at the Buck Institute have used RNA interference (RNAi) technology to identify hundreds of "druggable" molecular targets linked to the toxicity associated with the devastating, ultimately fatal disease. The results from this unprecedented genome-scale screen in a human cell model of HD are published in the November 29, 2012 edition of *PLOS Genetics*. The work was is a collaboration between Buck Institute faculty members Robert E. Hughes, Ph.D., Sean Mooney, Ph.D., Lisa Ellerby, Ph.D. and Juan Botas, Ph.D. at the Baylor College of Medicine.

HD is a devastating and incurable progressive neurodegenerative genetic disorder that affects motor coordination and leads to severe physical and cognitive decline. Currently, there are about 30,000 people in North America diagnosed with HD and another 150,000 people at risk for developing the disease. The disease pathology stems from a mutation in the huntingtin gene (HTT), resulting in the accumulation of a toxic protein leading to neuronal cell death and systemic dysfunction. Buck Scientists screened more than 7,800 genes pre-selected as potential drug targets to identify modifiers of HD toxicity in human cells, using technology that silences specific genes prior to analysis.

Lead author Robert Hughes said that among the diverse range of

modifiers identified, this study showed that RRAS, a gene involved in cell motility and neuronal development, is a potent modulator of HD toxicity in multiple HD models. "Our data indicates that the pathogenic effects of the HTT mutation on this pathway can be corrected at multiple intervention points and that pharmacological manipulation of RRAS signaling may confer therapeutic benefit in HD," Hughes said. Follow up work on the RRAS pathway is now underway in the Hughes lab and in the lab of Buck faculty member Lisa M. Ellerby, PhD.

Hughes said many molecular hits identified in the screening were validated in human cell, mouse cell and fruit fly models of HD – and that all the data from the study will be available to the public. "Our hope is that HD researchers will look at these targets and find modifiers relevant to the areas they already work on," said Hughes. "Ideally, pharmaceutical companies already working on some these pathways could build on their current knowledge and expertise by focusing their attention on the challenge to develop therapies for HD."

More information: Miller JP, Yates BE, Al-Ramahi I, Berman AE, Sanhueza M, et al. (2012) A Genome-Scale RNA–Interference Screen Identifies RRAS Signaling as a Pathologic Feature of Huntington's Disease. PLoS Genet 8(11): e1003042. doi:10.1371/journal.pgen.1003042

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