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The role of GSK-3 in DNA methylation: Relevance to bipolar disorder

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Glycogen synthase kinase-3 (GSK-3) activity has been shown to be a critical mediator of several signal transduction pathways, most notably Wnt and insulin signaling. Recently, we identified a novel function for GSK-3 in the regulation of DNA methylation. Using DNA methylation enrichment techniques followed by next-generation sequencing (methyl-seq), we identified thousands of genomic regions that have reduced DNA methylation when GSK-3 activity is absent or reduced. Lithium is a direct inhibitor of GSK-3 enzymes, and is also the primary therapy for the treatment of bipolar disorder (BPD). Little is known about how lithium treats BPD, but one of the leading hypotheses is that it is through GSK-3 inhibition. Based on this, we speculated that lithium could have its therapeutic effects via changes in DNA methylation. Toward this end, we have treated human cells with a GSK-3 inhibitor, and examined DNA methylation by performing methyl-seq. We identified and validated several loci that have also been implicated in BPD via genome-wide association studies (GWAS). In addition, we have performed methyl-seq on cells from individuals with BPD compared to unaffected siblings, and analyzed DNA methylation differences with methyl-seq. The results of these studies will be presented.

Biography

Phiel earned his B.S. in Biology from Ursinus College in 1992, and his Ph.D. from Thomas Jefferson University in 1998. He performed his post-doctoral fellowship with the Howard Hughes Medical Institute at the University of Pennsylvania from 1998-2003. Dr. Phiel was a Principal Investigator at Nationwide Children's Hospital and Ohio State University from 2003-2012, until recently moving to the University of Colorado Denver.

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