Spotlight on Science

Mapping Hydroxymethylation Patterns in Neurodegenerative Disease

Jonathan Mill, Ph.D.
Professor of Epigenetics,
University of Exeter
Medical School,
United Kingdom

What is the main focus of your research?

The main focus of our work is on understanding the causes and consequences of genomic variation in the brain, and the role this plays in neuropsychiatric and neurodegenerative disease. We are interested in understanding the changes in gene regulation that take place during development and aging of the brain, and the ways that this is influenced by genetic, environmental and stochastic factors.

What are some of the implications of methylation in neurodegenerative disorders?

We have identified some robust epigenetic signatures of diseases such as Alzherimer's disease. Interestingly, the changes we observe appear to be primarily seen in the cortical regions of the brain that are affected earliest and most severely in Alzheimer's disease and to a much lesser extent in regions of the brain like the cerebellum that are largely spared from neuropathological damage. We need to do further work to explore if the changes we observe are mechanistically-involved in the onset of neuropathology, or if they reflect a consequence of the disease process. We hope that the genes that we have found to be dysregulated will give us new insights about the underlying causes of dementia and possibly inform the development of novel therapeutic strategies.

How has detection of 5hmC been enabling?

Most of our early work used bisulfite-based sequencing data to map modified cytosine in the brain. Of course, we now know that this approach cannot distinguish between DNA methylation and hydroxymethylation. This limitation is particularly important to consider when studying the brain, given the higher levels of hydroxymethylation in regions like the cortex and cerebellum. The ability to quantify 5hmC at base-pair resolution has given us much better power to identify true epigenetic differences, and identify changes that were not detectable using standard bisulfite-based approaches. We have shown that there are very distinct patterns of 5hmC across different regions of the human brain, and that levels of this modification change very dramatically across brain development and aging. We are now studying levels of 5hmC within the context of diseases including Alzheimer's disease, autism and schizophrenia and finding some really remarkable differences associated with disease.

How has using TrueMethyl® oxBS better enabled your research?

We have been able to easily integrate this method with the array and sequencing-based approaches that we use to quantify DNA modifications. It means that we can quantify 'true' levels of both DNA methylation and DNA hydroxymethylation at base-pair resolution across

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the genome. I would certainly recommend this approach to anyone aiming to study DNA modification in human brain tissue; it's now clear that this is an abundant modification that could greatly confound studies using standard bisulfite-based approaches.

What is the ultimate goal of your work?

Ultimately, we plan to integrate multiple layers of gene regulation to better understand neuropsychiatric and neurodegenerative disease. The brain is an incredibly complex and heterogeneous tissue, and we are developing methods to assess genomic variation in specific neural cell populations isolated from different regions of the brain through development. Our hope is that by better understanding "normal" patterns of gene regulation in the human brain, and the way in which these change during development, aging and disease, we will learn more about the mechanisms underpinning disorders such as schizophrenia, autism and dementia.

To learn more about the research in Professor Mill's lab, please visit:

www.epigenomicslab.com

And check out these recent publications:

5-hydroxymethylcytosine is highly dynamic across human fetal brain development.
Spiers H, Hannon E, Schalkwyk LC, Bray NJ, Mill J.
BMC Genomics. 2017 Sep 18;18(1):738.
doi: 10.1186/s12864-017-4091-x.
PMID: 28923016

Variation in 5-hydroxymethylcytosine across human cortex and cerebellum.
Lunnon K, Hannon E, Smith RG, Dempster E, Wong C, Burrage J, Troakes C, Al-Sarraj S, Kepa A, Schalkwyk L, Mill J.
Genome Biol. 2016 Feb 16;17:27.
doi: 10.1186/s13059-016-0871-x.

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