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ALZHEIMER DISEASE

AD-susceptible brain regions exhibit altered DNA methylation

Alzheimer disease (AD) neuropathology is associated with distinctive changes in DNA methylation patterns, according to two reports recently published in *Nature Neuroscience*.

DNA methylation is a chemical modification—typically of CpG dinucleotides—that leads to gene silencing. Such modifications are said to be epigenetic, as they cause heritable changes in gene expression without altering the nucleotide sequence of the DNA.

> "The researchers found hypermethylation of ... *ANK1* ... in association with AD..."

In the first study, Jonathan Mill and colleagues initially performed an epigenome-wide association study (EWAS) in a discovery cohort of 122 brains from a London-based brain bank. "Because there is not necessarily a clear dichotomy between 'cases' and 'unaffected controls' in AD, we assessed the relationship between DNA methylation and quantitative measures of neuropathology, that is, neurofibrillary tangle burden and amyloid," explains Mill.

The researchers found hypermethylation of specific regions of the ankyrin 1 (*ANK1*) gene in association with AD neuropathology in the entorhinal cortex, a brain region that is known to be preferentially affected by AD. Similar hypermethylation was found in the superior temporal gyrus and prefrontal cortex, but not in the cerebellum, which tends to be spared by AD. The findings were confirmed in independent cohorts from two different brain banks.

The second study, which was led by Philip De Jager and David Bennett, confirmed the link between *ANK1* hypermethylation and AD neuropathology. In addition, the researchers found similar DNA methylation changes in a range of other genes, including *ABCA7* and *BIN1*, both of which had previously been found to harbour susceptibility variants for AD.

"Overall, these studies clearly demonstrate that epigenomic changes related to AD are not nonspecific, global changes from a systemic change in cell function," says De Jager. "Rather, a large but specific set of loci are involved, and we now have a robust set of loci with which to pursue mechanistic studies that would be impractical if they were conducted genome-wide."

Intriguingly, De Jager *et al.* found epigenomic changes in brains from individuals who showed no signs of cognitive impairment at the time of death but exhibited amyloid pathology on postmortem examination. This finding raises the possibility that altered methylation could be an early event in AD, although whether these changes are a cause or a consequence of the disease process remains to be established.

"These papers illustrate that interrogation of the methylome can yield novel insights into the genetic basis of AD," concludes Bennett. "The epigenome is modifiable and offers a potential mechanism whereby experience can alter brain function." The new findings should provide a basis for further investigations into the interaction between environmental and genetic factors in determining AD susceptibility.

Heather Wood

Original articles Lunnon, K. *et al.* Methylomic profiling implicates cortical deregulation of *ANK1* in Alzheimer's disease. *Nat. Neurosci.* doi:10.1038/nn.3782 | De Jager, P. L. *et al.* Alzheimer's disease: early alterations in brain DNA methylation at *ANK1*, *BIN1*, *RHBDF2* and other loci. *Nat. Neurosci.* doi:10.1038/nn.3786