



News

Drifting Toward AD—Epigenetic Changes Linked to Disease

23 July 2008. You can't do anything about the genome you were born with, but you may be able to change your epigenome—the complement of chemical modifications that influence how, when, and where the genetic code is put to use. Epigenetic changes have been linked to a variety of diseases, including schizophrenia, bipolar disorder, and now, Alzheimer disease (AD). In the July 16 PloS ONE, researchers led by Axel Schumacher at the Klinikum rechts der Isar, Munich, Germany, report that epigenetic drift, or change, that occurs with age may put people at higher risk for developing the disease. The findings suggest that epigenetic drift may be an important driving force in AD pathology and raise the tantalizing question of whether such epigenetic changes could be prevented. “My guess is yes,” Schumacher said in an interview with ARF, but he cautioned that we simply do not know enough yet about epigenetics to determine exactly how this could be achieved.

There is some evidence pointing to a role for epigenetics in AD pathology. For example, the age of onset and pathology seen in identical twins genetically predisposed to dementia can differ substantially (see [Brickell et al., 2007](#)). This can be better explained by epigenetic factors than genetic ones (see [ARF related news story](#)). One of the major epigenetic changes in the genome is methylation—the addition of small methyl groups to the individual bases that make up the genetic code. Cytosine-guanine (CpG) “islands” are hot spots of methylation and can turn gene activity up or down depending on their degree of modification. Schumacher and colleagues examined CpG islands in DNA loci that have been linked to AD susceptibility. First author Sun-Chong Wang and colleagues used mass spectrometry to examine CpG methylation in 12 loci, including those harboring genes for amyloid- β precursor protein, β -secretase, γ -secretase components, and ApoE. They examined DNA in lymphocytes and also in postmortem brain tissue from late-onset AD patients and controls.

Wang and colleagues found that for all 12 loci, the “epigenetic distance,” or the absolute difference between methylation at a given site in an individual compared to the norm, was generally higher in LOAD patients. In fact, nine out of 10 of the most abnormal methylation patterns were found in LOAD patients. Though there was generally a low interindividual difference in the pattern of methylation, CpG islands in four genes showed moderate to large differences. Two of the four genes, DNMT1

(DNA methyl transferase 1) and MTHFR (methylenetetrahydrofolate reductase), are involved in regulating methylation status, and the other two, APOE and PSEN1, are well-known risk genes for AD. “It is very interesting that the genes which are the main predisposing factors for Alzheimer’s disease, PSEN and APOE, have the highest interindividual variation, which could indicate they are prone to epigenetic abnormalities,” said Schumacher. “Depending on where each person carries methylation groups, that person may have very different predispositions to the disease. This is one branch of research that has to be followed up to see if it bears out in large scale,” he said.

Comparing methylation patterns with age, the researchers found that epigenetic distance did not change with age in controls but increased in LOAD patients. In some loci the increasing epigenetic distance resulted from a combination of age-related decrease in methylation in controls versus an increase in LOAD patients, or vice versa. Methylation of APOE, for example, decreased in normal brain by 10.6 percent over 30 years, whereas it increased in LOAD brain by 6.8 percent over the same time frame.

Wang and colleagues carried out detailed statistical analysis to determine if any methylation pattern changes might be diagnostic for LOAD. They found that though the changes were relatively small (around 10 percent change in methylation level) age-related epigenetic drift was significant for APOE and [TFAM](#) (transcription factor A, mitochondrial). CpG islands in the PSEN1 gene were associated with stronger methylation differences but only in a subset of patients, perhaps reflecting the fact that PSEN1 exhibits some of the highest methylation variation of all the genes studied.

The study suggests that epigenetic difference could have an influence on the incidence or progression of AD. “I’m sure that genetic mutations will probably explain 5-10 percent of all cases of Alzheimer’s disease, and I would expect that for a large number of patients we find nowadays in the clinics, the cause is something else. My guess is that most of them might have some epimutations due to slow epigenetic drift or to other events in the genome,” said Schumacher. Those events can span a lifetime, or more. As the authors write, “In our model, the epigenetic effects can accumulate throughout life, especially from the time-point when the epigenetic machinery suffers from old age, but also from early embryonal stages or even trans-generational, influenced by epigenetic events in the parents.” Recent work from a group in Iceland also supports the idea of widespread methylation changes and even indicates that they may be under genetic control (see [ARF related news story](#)). It should also be kept in mind that the researchers base their findings on whole tissue samples, and it is possible that epigenetic drift is even more marked within individual cells. Currently, it is not possible to map methylation patterns in DNA derived from

single cells, but Schumacher said he expects that may soon change as the technology improves.

If epigenetic changes can predispose individuals to AD, then is there any way to limit that risk or prevent such epimutations from taking place? “I have absolutely no doubt that there are components of western diet that affect methylation patterns. We are only slowly gaining knowledge about what is affecting our epigenome, and this is one field of study that we need to put a lot more resources into,” said Schumacher. A case in point is a recent study linking the advent of western diet in Iceland with a dramatic reduction in lifespan in people with an inherited form of cystatin C amyloid angiopathy, a progressive, fatal, hemorrhagic disease (see [ARF related news story](#)).—Tom Fagan.

Reference:

Wang S-C, Oelze B, Schumacher A. Age-specific epigenetic drift in late-onset Alzheimer’s disease. PLoS One 2008, July; 3:e2698. [Abstract](#)

Comment

Comment by: George M. Martin (ARF Advisor)

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I am delighted that Wang and colleagues have done such a detailed analysis of the epigenome in LOAD. The results, especially the evidence of particularly marked epigenetic drifts in PS1 and APOE, are of great interest. The authors wisely point out, however, that there is an underlying methodological problem—variable shifts in subpopulation heterogeneity—and point out the need for follow-up studies using such methods as laser-assisted microdissection and single cell analysis.

While these results are likely to reflect, at least in part, variable environmental impacts, I am increasingly impressed with the potential role of stochastic events that can lead to epigenetic drifts in gene expression. There is enormous intra-specific variability in longevity within model organisms for which both genotype and environment appear to have been well controlled. This leads me to conclude that, while nature, nurture, and chance all play roles in modulating the rates of aging and the rates at which late-life disorders emerge, for the case of variations *within* a species, **[...continued]** the "800-pound gorilla" may well be chance, including varying patterns of epigenetic drift. This is in striking contrast to the dominating role of the constitutional genome in the modulation of lifespan and late-life disorders *between* species. A question of great interest is the implications that one might derive from evidence that random variations in gene expression have

deep evolutionary roots (e.g., in bacteria). Given unpredictable environments, it might be adaptive for a population to have not only genetic heterogeneity but also epigenetic heterogeneity. Perhaps LOAD is an antagonistic pleiotropic byproduct of a class of gene action that has beneficial effects on younger, reproducing populations; the price we pay may be unlucky members of our aging population who have had their epigenetic changes drift in the wrong directions. I hope to live long enough to test my more general quasi-group-selectionist hypothesis!