Proposal für einen neuen Forschungsantrag im Rahmen des Diet, Body, Brain (DietBB) Konsortiums (BMBF Ausschreibung Kompetenzcluster Ernährungsforschung, Sprecherin U. Nöthlings, Bonn).

Epigenetics, nutrition, and risk of cognitive decline and Alzheimer disease in old age

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Das Proposal wurde wie vorgelegt in AgeCoDe/AgeQualiDe TK 5 am 10.03.2014 genehmigt. Da die Blutanalysen unter Bonner Schirmherrschaft vorgenommen und im Rahmen der AgeCoDe Fragestellungen ausgewertet werden, sind die unterzeichneten Einverständniserklärungen der Probanden für die angestrebten Auswertungen gültig.

Die Antragsteller werden gebeten die AgeCoDe Study Group über den aktuellen Stand der Anträge und ggf. des Projektes auf dem Laufenden zu halten.

Rationale and background:

A growing body of evidence supports the hypothesis that Alzheimer's disease (AD) not only results from the combined effects of variation in a number of genes and environmental factors, but also from epigenetic abnormalities such as histone modifications or DNA methylation. Interestingly, some known environmental factors linked to AD play also a role in the regulation of epigenetic mechanism.

Epidemiological data have suggested a link between dietary patterns and risk of AD. This includes saturated fatty acids, monounsaturated fatty acids, ω-3 polyunsaturated fatty acids, ω-6 PUFA, vitamin E, vitamin B12, and folate. Several of these nutrients are included in the so-called Mediterranean diet (MeDi) which has been link to protection against AD. However, the underlying mechanism of this interaction is still unknown. On the other hand, dietary deficiency or malabsorption of vitamin B12, B6, and folate create a lower methylation potential which may lead to aberrant DNA hypomethylation. This provides a putative molecular link between epigenetic mechanisms and the protective role of MeDi against AD.

Objectives:

The present study aims at the identification of methylation signatures predicting risk of developing AD and how MeDi modulates these signatures to protect against incident AD. In addition, we will investigate the effect of MeDi upon rate of cognitive decline through modulation of DNA methylation.

Methods:

We have generated genome-wide methylation data in 200 DNA samples using the Illumina Human Methylation450K BeadChip. The 200 samples comprised a total of 100 individuals from the prospective AgeCoDe cohort for whom DNA was available at baseline and at follow up 3 (3 years later), i.e. a total of 200 DNA samples. From these 100 individuals without dementia at baseline, 45 participants developed dementia at follow-up 3. The control sample comprises 55 persons that do not have dementia at baseline and at follow-up 3. These controls were matched with the AD sample for age, gender, and APOE genotype. Genome-wide patterns of methylation will be searched that are differentially methylated between the AD and the control samples. The modulation produced in this methylation patterns by environmental factors including nutritional will be explored systematically. We will also explore the modulating role of genetic variants in these loci by screening genetic variants within the linkage disequilibrium block containing the differentially methylated sites.

Expected results:

An AD methylation signatures will be identified predicting risk of developing AD and the speed of the cognitive decline. These signatures are modified by nutritional patterns modulating thereby the risk of AD.

Innovation:

This unique setup will identify an epigenetic signature associated with incidence of AD and it modulation by nutrition. This will provide a most valuable resource for the development of novel

biomarkers for AD. Because epigenetic changes are reversible, identification of methylation changes associated with incidence of AD will offer, from a therapeutic perspective, a strong candidate target for individuals at risk.