Environmental influences on gene networks of cognitive aging: how sex and ApoE interact with ambient air pollution (AAP) and cigarette smoke (CS)

Authors: Amin Haghani¹, Mafalda Cacciotolo¹, Kevin Doty², Constantinos Sioutas³, Terrence Town², Todd E Morgan¹, Levine Morgan⁴, Caleb E Finch¹*

¹, Leonard Davis School of Gerontology, University of Southern California, Los Angeles, CA.  
², Zilkha Neurogenetic Institute, University of Southern California, Los Angeles, CA.  
³, Viterbi School of Engineering, University of Southern California, Los Angeles, CA.  
⁴, Department of Pathology, Yale School of Medicine  
*Corresponding author. Email cefinch@usc.edu.

Background: Inhaled toxins from CS and AAP are major risk factors of Alzheimer disease (AD) (1,2). However, potential interactions with sex and ApoE alleles are obscure. This novel analysis identifies pathways of GxE interactions for CS and AAP with sex and ApoE alleles that increase risk of accelerated cognitive aging and AD.

Methods: Associations of sex, ApoE allele, and CS with cognitive age were examined in the Health and Retirement Study, a US-wide study of health and aging that identified a gene network of older CS smokers (3). The sex-apoE analysis for CS and cognitive aging in HRS was extended to a mouse model of AAP, ApoE targeted replacement mice with exposure to nano-sized AAP (nPM).

Results: In HRS, cognitive aging was associate with CS, with greater male vulnerability but no ApoE allele interaction. Mouse transcriptome showed differential expression of 222 genes in CS survivors (3) with nPM:sex interactions associated with inflammation. Analysis of sex chromosome-linked genes identified a subset that could derive GxE expression response to nPM on somatic chromosomes. Weighted gene co-expression analysis of (WCGNA) identified two network modules associated with longevity and neural functions, that included many AD-associated genes. These modules had higher female response to nPM, particularly for ApoE3.

Conclusion: AD and cognitive decline phenotypes are shaped by the GxE interaction of ApoE genotype and airborne toxins with sex differences. While HRS cognitive data suggested higher male vulnerability to smoking, mouse transcriptome data showed female vulnerability to AAP in AD-associated genes. Epidemiological data from HRS may represent male smoking behavior more than biologically seated sex:CS interaction. The cerebral cortex transcriptome and network modules show deep interactions of sex and ApoE alleles with airborne toxins. These findings are relevant to AD clinical trials which have ignored individual exposure to CS and AAP. We suggest that clinical trials for AD drugs include CS, AAP, and GxE interactions for other AD risk genes besides ApoE4.

1, Cacciotolo et al 2017, PMID 28140404; 2, Durazzo et al 2014 PMID 2492655; 3, Levine and Crimmins, 2016 PMID 26355015. We appreciate NIA support, P01-AG055367.