Title: Genome-wide Association Study of Susceptibility to Particulate Matter-Associated QT Prolongation

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Topic

Background: Exposure to ambient particulate matter (PM) air pollution has been associated with increases in QT interval duration (QT). However, genetic susceptibility to PM-associated QT-prolongation has not been characterized.

Methods: To characterize such susceptibility in a genome-wide association study, we conducted cohort-, race/ethnicity-, and sex-stratified longitudinal analyses of nine Women's Health Initiative clinical trials and Atherosclerosis Risk in Communities Study subpopulations (total n: 22,158). We used generalized estimating equations methods adapted for low prevalence exposure to estimate approximately 2.5 million SNP x PM_{10} interactions for each subpopulation while adjusting for age, geographic region or center, season, calendar year, RR interval, and ancestry. We then combined results using fixed-effects, inverse variance-weighted meta-analysis.

Results: A common variant (rs1619661; coded allele [T] frequency: 81-92%) significantly modified the association between QT and PM_{10} concentration ($P = 2.11 \times 10^{-8}$). At PM_{10} concentrations > 90^{th} percentile, QT increased 7 ms across the CC and TT genotypes: from 397 (95% confidence interval, 396, 399) to 404 (403, 404) ms. However, QT changed only slightly across rs1619661 genotypes at lower PM_{10} concentrations. The rs1619661 variant is on chromosome 10, 132 kb downstream from *CXCL12* which encodes a chemokine, stromal cell-derived factor 1 (SDF1), that is expressed in cardiomyocytes and decreases β-adrenergically activated calcium influx across the L-type Ca^{2+} ion channel, an effect reversed by β-antagonists.

Conclusions: Biologically plausible genetic factors may alter susceptibility to PM_{10}-associated QT prolongation in racially, geographically and environmentally diverse populations protected by U.S. EPA National Ambient Air Quality Standards.