GENOME-WIDE INTERACTION STUDY OF CUMULATIVE PARTICULATE MATTER EXPOSURE ON AGE-RELATED LUNG FUNCTION DECLINE IN ADULTS, THE SAPALDIA COHORT.

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Background and Aims: Air pollution exposure accelerates age-related lung function decline. There is however evidence that i) genetic variation in individuals determines the susceptibility to ambient air pollution and ii) asthmatics are more prone to accelerated lung function decline than non- asthmatics. We investigated the interaction of genome-wide data with particulate matter (PM) exposure on the annual rate of lung function decline in an agnostic approach.
Methods: 2'500K single nucleotide polymorphisms (SNPs) of 455 asthmatic and 699 non-asthmatic SAPALDIA participants with individual exposure data for 11-year cumulative PM of mean diameter <10µm (PM10) was used. Annual rate of lung function decline (•) was calculated for five spirometric parameters (FEF25-75, FEV1, FVC, FEF25-75/FVC, FEV1/FVC). They were regressed on PM10, the SNP allele dosage and their interaction term adjusting for study center, sex, height, age, packyears, asthma self-report and ancestry informative covariates. We also stratified analyses by asthma status. Only SNPs with minor allele frequency (MAF) >5% were considered.
Results: In both groups combined, the top-ranking interaction signal was observed for • FEV1 ($P=4.07x10^{-8}$; MAF:6%) and contained genes *CRHR2/INMT*, both involved with lung health. Another prominent signal for • FEF25-75 was in *TRAM2*, a gene involved in collagen synthesis ($P=8.78x10^{-8}$; MAF 37%).
In non-asthmatics, a highly prevalent variant (MAF:45%) at 7q22.1 was a top-ranking interaction signal and reached $P=4.15x10^{-9}$ for • FEF25-75 (rank1), $1.31x10^{-6}$ for • FEF25-75/FVC (rank10), $3.08x10^{-6}$ for • FEV1 (rank73) and $6.98x10^{-7}$ for • FEV1/FVC (rank12).
In asthmatics, the top-ranking locus interacting with PM10 ($P=7.27x10^{-12}$, MAF: 8%) contained genes *MYO15A* , necessary for cilia function, and *DRG2*, expressed in normal fibroblasts and linked to the infectious disease progression. Variation in a locus *ZDHHC19/OSTalpha/PCYT1A* (MAF:20%) was interacting with PM10 exposure on • FVC and • FEV1 ($P=9.82x10^{-9}$; $P=1.05x10^{-8}$).
Conclusions: This preliminary evidence of interactions requires replication within the SAPALDIA cohort (N=4000) and collaborative efforts with other studies.

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