Oxidative stress pathway genes, particulate matter, and lung function decline

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Background and Aims

Rather than investigating gene-environment interactions with single nucleotide polymorphisms (SNPs), ambient air pollution and smoking effects on lung function decline might be better explained by assessing interactions across entire genes and pathways.

Methods

Decline in forced expiratory volume in one second (FEV1) was regressed on 11-year cumulative exposure to particulate matter <10µm in diameter (PM10) or packyears of smoking, additive SNP effects, and a multiplicative term SNP*exposure in 669 adults from the SAPALDIA cohort. Interaction p-values of 12'679 SNPs from 152 oxidative stress genes and 14 pathways were projected onto gene- and pathway-levels using the adaptive rank truncation product (ARTP) method. Effect estimates for one interquartile range (IQR) contrast in exposure were compared between PM10 and packyears for top-SNPs of significant genes (significance threshold alpha=0.05). Percentage of outcome-variability explained was calculated by including all top-SNPs and interaction terms simultaneously into initial regression models.

Results

Seven genes (*CP, CYP1A2, ERCC1, NDUFA13, PRDX3, PSMB5, RAC1*) significantly interacted with PM10 on FEV1 decline, seven other ones (*AOX1, BCL2, MAP2K1, NOXO1, PSEN1, PTK2B, TPO*) and pathway 'apoptosis' (p=0.001) with packyears. A change of 84.7µg/m^3*years PM10 over 11 years (IQR) yielded beta-estimates of 41.7-97.7ml for the interaction term, 134.4-321.9ml for SNPs, and 20.6-134.6ml for PM10 main effect, with a minimal $p_{interaction}=4.8x10^{-5}$. Corresponding estimates for an IQR of 9.7 packyears were 86.2-206.6ml, 28.0-51.6ml, 23.4-288.6ml, and $p_{interaction}=9.8x10^{-5}$. Full interaction models explained 24.9% outcome variability for PM10, 26.4% for packyears, and 30.7% for both exposures combined compared to 19.6% and 19.1% without interaction terms, and 19.9% without genetic factors.

Conclusions

Including gene environment interaction in a pathway analysis substantially increased the percentage of explained outcome variability. On the population level, PM10 exposure presented a similar impact on FEV1 decline as tobacco smoke regarding effect sizes and percentage variability explained, but susceptibility genes differed between exposures.