Association of *APOL1* Risk Genotype and Air Pollution for Kidney Disease

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Significant disparities exist in kidney disease, with blacks facing a higher burden of CKD and kidney failure. In addition to socioeconomic/health system factors, these disparities are linked to two sequence variants (G1 and G2) in the apoL1 (*APOL1*) gene. The high-risk *APOL1* genotype (two copies of variants), present in up to 16% of blacks but <1% of Europeans (http://apol1.org/), is associated with an increased risk for CKD (1,2). However, the *APOL1* high-risk genotype has incomplete penetrance and only some individuals with the high risk genotype develop overt kidney disease, indicating the presence of genetic/environmental modifiers (*i.e.*, "second hits"). Thus, investigations into nontraditional/emerging risk factors are necessary to explore what modifies genetic risk.

Air pollution measured by fine particulate matter <2.5 μm ($PM_{2.5}$) is an emerging robust risk factor and CKD/kidney failure risk increases linearly with $PM_{2.5}$ (3). We hypothesized that like other chronic diseases, environmental risk ($PM_{2.5}$) interacts with genetic risk (*APOL1*) to increase kidney disease. We utilized a large, biobanked cohort (Bio*Me* Biobank at Mount Sinai) with linked genetic, clinical, and residential history information to reconstruct environmental exposures. We included 4800 participants self-identifying as black enrolled at a large, quaternary care health system in New York City serving an urban population from all boroughs and New Jersey. The mean age was 51 years, 63% were women, 29% had a history of type 2 diabetes (T2D), and 62% had a history of hypertension. *APOL1* high-risk genotype was defined as two risk variants and low-risk genotype was defined as one or zero risk variants. We mapped the residences of participants to city blocks and estimated average $PM_{2.5}$ exposure in the year before enrollment, using a previously developed model combining satellite-derived aerosol optical depth retrieval with land use, meteorology, and spatially derived features (4). Finally, we identified CKD stage 3 or higher using a validated algorithm (5), and kidney failure using US Renal Data System linkage over follow-up. We defined a composite kidney outcome as either CKD stage 3 or higher or kidney failure (Figure 1).

Of 4800 blacks with 5.4 median follow-up years, 675 (14%) had *APOL1* high-risk. There were 1286 blacks with the composite outcome and 293 with kidney failure; 253 (37%) individuals in the *APOL1* high-risk group and 1033 (25%) in the low-risk group had the composite kidney outcome. Compared with low-risk *APOL1* individuals, high-risk *APOL1* individuals had a significantly lower eGFR at enrollment (75 versus 82 ml/min per 1.73 m^2; $P<0.001$), higher proportion of kidney outcome (37% versus 25%; $P<0.001$), and hypertension (66% versus 61%; $P=0.03$). We evaluated statistical significance using the chi-squared test and *t* test for categorical and continuous variables, respectively. There were no significant differences in BMI (31.3 versus 30.7; $P=0.08$), age (51 versus 51 years; $P=0.45$), sex (63% versus 63% female; $P=0.98$), T2D (31% versus 29%; $P=0.43$), or $PM_{2.5}$ (12.1 versus 12.2 $\mu g/m^3$; $P=0.61$) concentrations between *APOL1* high- and low-risk.

We investigated the *APOL1*–$PM_{2.5}$ interaction using a logistic regression model adjusted for age, sex, ten genetic principal components, Medicaid status, T2D, and enrollment eGFR with an *APOL1*–$PM_{2.5}$ interaction term to generate adjusted odds ratios (aORs) and 95% confidence intervals (95% CIs). First, there was a significant association with outcome for $PM_{2.5}$ and *APOL1* individually. We found an increased aOR of 1.07 (95% CI, 1.01 to 1.15; $P=0.02$) for every 10 $\mu g/m^3$ increase in $PM_{2.5}$ and 1.12 for *APOL1* high-risk (95% CI, 1.09 to 1.16; $P=1.3\times10^{-11}$). We also found a significant interaction between $PM_{2.5}$ and *APOL1* ($P<0.001$). In individuals with *APOL1* high-risk, we observed increased aOR of 1.54 (95% CI, 1.32% to 1.80%; $P=1.1\times10^{-7}$) for every 10 $\mu g/m^3$ increase in $PM_{2.5}$. In contrast, in *APOL1* low-risk, we found an increased aOR of 1.11 of kidney outcome (95% CI, 1.05 to 1.17; $P=1.9\times10^{-4}$) for every 10 $\mu g/m^3$ increase in $PM_{2.5}$. Thus, slope of $PM_{2.5}$ exposure for *APOL1* high-risk is steeper than that for low-risk individuals, suggesting a multiplicative interaction (Figure 1B).

This suggests that, although both $PM_{2.5}$ and *APOL1* independently increase kidney disease in blacks, the effect of $PM_{2.5}$ is worse in *APOL1* high-risk individuals. Thus, although *APOL1* high-risk genetically predisposes individuals for kidney disease, environmental exposures may serve as a second hit that accentuates this. This may partially explain the incomplete penetrance of *APOL1* wherein interplay between genetic and

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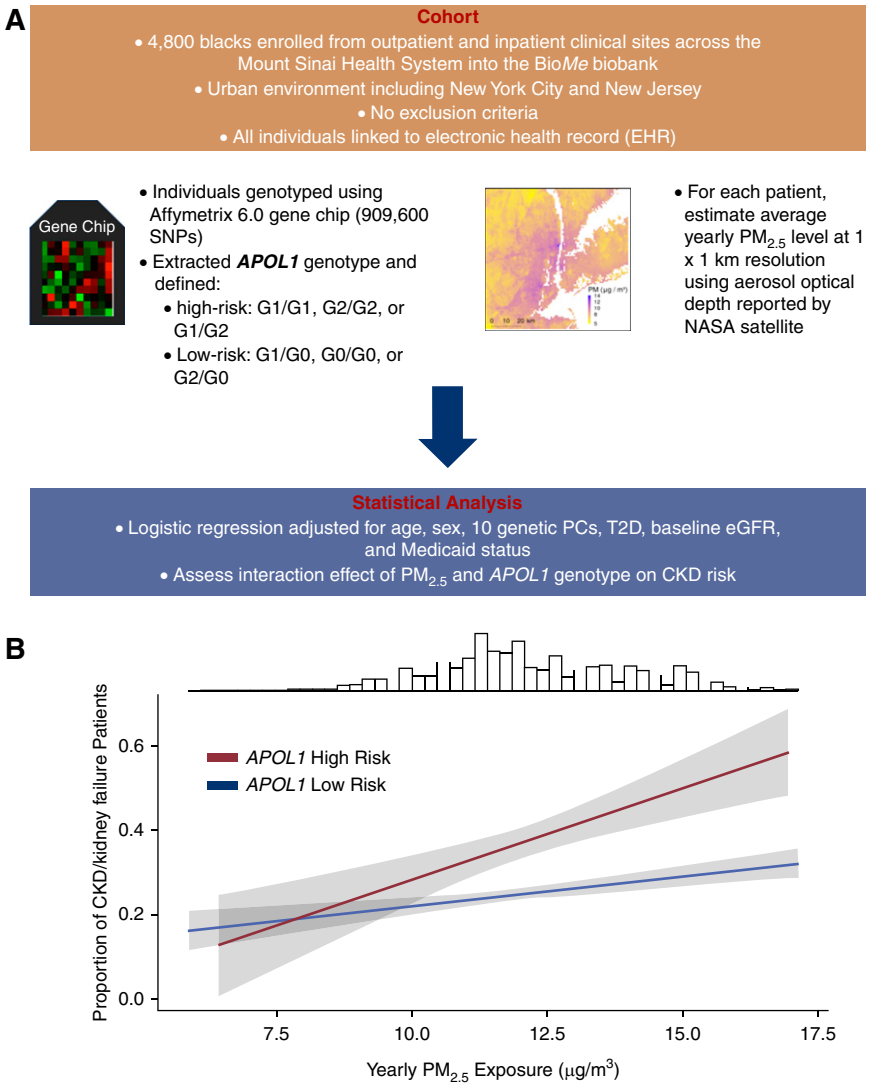

Figure 1. | **Study methodology and APOL1 interaction for CKD risk.** (A) Flowchart of methodology used in this study. (B) Proportion of CKD/kidney failure stratified by *APOL1* genotype with higher average $PM_{2.5}$ exposure in the year before enrollment. Shaded gray regions represent 95% confidence intervals obtained from a logistic regression model adjusted for age, sex, body mass index, 10 genetic principal components, history of type 2 diabetes, Medicaid status, and baseline eGFR. For purposes of visualization of the slopes, the values of continuous predictors are computed at the cohort mean of each covariate. Frequency distribution at top represents the distribution of mean $PM_{2.5}$ in our cohort. NASA, National Aeronautics and Space Administration; PC, principal component; $PM_{2.5}$, fine particulate matter <2.5 μm; T2D, type 2 diabetes.

environmental factors influence kidney risk. Limitations include lack of replication, complete personal exposure data, enrollment albuminuria and detailed socioeconomic information. Additionally the cross-sectional nature of our study may not capture the effect of varying $PM_{2.5}$ exposure over time. Further, as we defined the composite outcome as both prevalent/incident CKD and kidney failure, it is possible that $PM_{2.5}$ exposure in the year before enrollment contributes more to incident than prevalent CKD. If replicated, it would represent the first example where a common genotype interacts with a common environmental exposure for kidney disease and exacerbates ethnic disparities.

In conclusion, in a cohort of 4800 blacks we demonstrated a significant interaction effect between *APOL1* high-risk genotype and $PM_{2.5}$ for kidney disease.

Disclosures

Dr. Nadkarni is cofounder of and owns equity in Pensieve Health and is a cofounder and member of scientific advisory board of and owns equity and options in RenalytixAI. Dr. Nadkarni also reports receiving consulting fees from AstraZeneca, BioVie, Inc., GLG Consulting, and Reata Pharmaceuticals. Dr. Bottinger, Dr. Chaudhary, Dr. Cooper, Dr. DeFelice, Dr. Glicksberg, Dr. Horowitz, Mr. Jaladanki, Dr. Just, Mr. Kapoor, Dr. Manna, Mr. O'Hagan, Mr. I. Paranjpe, and Mr. M. Paranjpe have nothing to disclose.

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