emerge network

eMERGE Network: Manuscript Concept Sheet

Reference Number *(to be assigned by CC)*	NT479
Submission Date	6/22/23
Project Title	The protective effect of the APOL1 p.N264K variant in APOL1 G2-associated kidney disease
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Sites Participating	All other eMERGE sites are invited to participate
Background / Significance	African Americans develop kidney disease at a rate five times higher than Americans of European ancestry. This excess burden of kidney disease is largely mediated by two variants (G1 and G2) in the apolipoprotein L1 (APOL1) gene. The number of at-risk individuals for APOL1 nephropathy is enormous; it is estimated that 13% of Black Americans carry two high-risk alleles (APOL1-HR), and in certain West African populations, the rate of high-risk genotypes is as high as 20-25%. However, at most 15% of individuals with a high-risk genotype will go on to develop kidney failure. This incomplete penetrance is thought to likely reflect a requirement for disease modifiers that affect APOL1 cytotoxicity. In 2019, we studied to cytotoxic effect of multiple naturally and non-naturally occurring APOL1 haplotypes and found that the toxicity of G1 and G2 alleles was dramatically reduced when expressed on the haplotype defined by the APOL1 missense variant p.N264K.
Outline of Project	Here we will test the hypothesis that the naturally-occurring APOL1 p.N264K missense variant represents a protective allele for APOL1-mediated kidney disease. We set up a set of genetic association studies for the p.N264K variant among APOL1-HR subjects to confirm its protective role. We have already conducted a genetically matched association study on 528 APOL1-HR FSGS cases and 2,606 APOL1-HR controls and found that the p.N264K confers a striking 10-fold protection against APOL1-associated FSGS. We next replicated these findings in the REGARDs cohort, where the p.N264K missense variants protects against kidney disease at different severity stages. We are now proposing to replicate these results in eMERGE-III and All-of-Us datasets. Within eMERGE-III, we propose to identify all individuals who are APOL1-HR, and test for the effect of the p.N264K missense variant on the CKD outcome in this subgroup.
Desired Data - Common Variables* *(Available from the CC)*	☒Demographics ☒ICD9/10 codes ☒CPT codes ☒Phecodes ☐BMI ☒Common Variable Labs ☒Common Variable Meds ☐ Geocoding 2015 ACS variables' ☒Other: Case/Control status on Phase I-III phenotypes

Other Desired Data *(Available from participating sites)*	*Please specifically list out any data elements that participating sites would collect or extract from clinical or other sources for this project (i.e. not common variables above)*
Desired Genetic Data	☒eMERGE I-III Merged set (HRC imputed, GWAS) ☐eMERGE PGx/PGRNseq data set ☐eMERGEseq data set (Phase III) ☐eMERGE Whole Genome sequencing data set ☐eMERGE Exome chip data set ☐eMERGE Whole Exome sequencing data set ☐Other (not listed above):
Does project pertain to an existing eMERGE Phenotype?	☒Yes, if so please list: CKD Phenotype ☐No
Planned Statistical Analyses	We will extract all individuals of African ancestry (by genetic ancestry classification) with HR APOL1 genotype. We will then phenotype these subjects for CKD and stage kidney disease among the cases. We will then use logistic regression to test the effect of p.N264K missense variant on CKD (by stage) among African ancestry individuals with HR genotype as a whole, and by APOL1 HR genotype class (G1G1, G1G2, G2G2). We will adjust for age, sex, and PCs of ancestry. These results will be meta-analyzed with the REGARDS, All-of-Us, and other cohorts.
Ethical Considerations	N/A
Target Journal	Depending on the final results, potentially Nature Medicine or a general medical journal
Milestones *(This section should include the key dates for completion of project, including approval, project duration, draft completion, and submission.)*	All discovery elements of this project have already been completed. We anticipate <1 month for the completion of the proposed replication studies since no new data is being generated as part of this proposal. Anticipated manuscript submission: within 1-3 months.

*Common Variables available across all datasets:

- Demographics: sex, year of birth, decade of birth, race, ethnicity
- Codes: (repeated values & age at event): ICD, CPT, Phecodes
- BMI: (repeated value & age at event) height, weight, BMI
- Labs: (lab name, repeated lab value & age at event) Serum total cholesterol, LDL, HDL, Triglycerides, Glucose fasting/non-fasting/unknown, & White Blood Cell count
- Medications: (medication name, repeated, & age at event) Cerivastatin sodium, Rosuvastatin, Simvastatin, Fluvastatin, Pravastatin, Lovastatin, Atorvastatin, & Pitavastatin
- Other: Case/Control status on Phase I and Phase II phenotype: only on GWAS dataset participants