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EDITORIAL COMMENT

Apolipoproteins and Blood Pressure

A Story of Evolution in Biomarker Analysis*

Camilo Fernandez, MD, MSc, MBA,[a,b] Alexander Romero, MD,[c] Thomas D. Giles, MD[b]

The 1930s marked the beginning of the "golden age" in cardiovascular disease biomarker research (1). Lipoproteins and blood pressure (BP) are 2 such biomarkers that have attracted the attention of many investigators around the globe. A wealth of data has accumulated over the years providing the groundwork for the development of both diagnostic and therapeutic arenas. It is now recognized that these biomarkers—lipoproteins and BP—are major contributors to cardiometabolic and renal disease risk over the course of life (2,3). Data concerning the race-related interactions of these 2 two biomarkers are scarce.

The continuing interest in disease pathogenesis at the molecular level has created a demand for in depth analysis of population data of biomarkers. An example is the interaction of the apolipoprotein L1 gene (*APOL1*) variants with BP and the race-dependent association with end-organ damage, particularly the kidney (4). Contemporary molecular genetics techniques have already demonstrated that variation in *APOL1* explains the excess risk and higher prevalence of nondiabetic end-stage renal disease (ESRD) in African Americans (AAs), compared with individuals without recent African ancestry. *APOL1* risk alleles confer resistance to *Trypanosoma brucei* infections in Sub-Saharan Africa, resulting in their positive selection and significantly higher frequency in individuals of African ancestry (5).

In this issue of the *Journal,* the original investigation by Nadkarni et al. (6) elegantly demonstrates the association of *APOL1* with BP. The authors utilize genomic data to test the interdependence of *APOL1* G1 and G2 risk alleles with BP traits and renal function. The study involved 5,204 AA subjects with predominantly African genetic ancestry. These subjects were enrolled in the Mt. Sinai Bio*Me* biobank, including additional Bio*Me* (n = 1,623), Vanderbilt BioVU (n = 1,809), and Northwestern NUgene (n = 567) AA biobank subjects. The study found that age at diagnosis of hypertension was 2 to 5 years earlier among those with homozygous *APOL1* and that subjects with this gene variant, in the 20- to 39-year age group, had higher systolic BP—regardless of absence or presence of treatment. In addition, *APOL1*-associated decline in renal function was observed in the 30- to 39-year age group. The authors concluded that *APOL1* genetic testing could be helpful in identifying young individuals of African ancestry with increased BP burden and increased risk for hypertension-related cardiovascular and renal damage.

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Despite the intuitive structural design of this study by Nadkarni et al. (6), noteworthy limitations exist. The use of office-based BP measurements—as opposed to 24-h ambulatory BP monitoring—in defining the hypertension phenotype constitutes, in our view, the main limitation. Office-based measurements may not reflect the true BP levels (7) and often present variation depending on the methodology utilized for its assessment (8). Recorded BP may be elevated when the usual BP is normal (white coat effect), or recorded BP may be normal when the usual BP is elevated (masked hypertension). Office measurements also do not reflect the diurnal and nocturnal variability in BP levels (9–11). Similar analyses utilizing 24-h ambulatory BP monitoring as an

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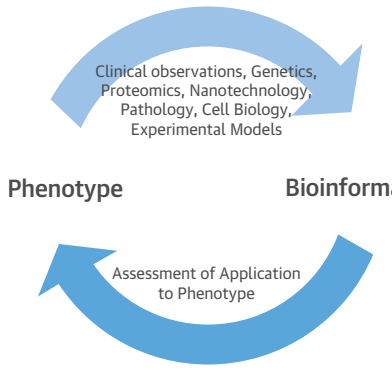
From the [a]HeartGEN Institute, Boston, Massachusetts; [b]Heart and Vascular Institute, Tulane University School of Medicine, New Orleans, Louisiana; and the [c]Section of Cardiology, St. Thomas Hospital, Panama City, Panama. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

FIGURE 1 Continuous Phenotypic Refinement



Proposed pathway for the biotechnological integration of multiple subject-specific characteristics to enhance phenotypic classification.

outcome measurement may help confirm the findings of this study.

Another limitation of this study is the small number of participant characteristics used in the analyses. This may not entirely be in connection with the main purpose of the study, but it surely contributes to strengthening its conclusions and outlook. A greater number of characteristics facilitates the refinement of the analyses by employing techniques such as continuous phenotypic refinement (CPR) to enhance the predictive ability of the determinants (in this case, genetic) and its association with the outcome(s) of study (in this case, phenotype). CPR constitutes a highly-integrated approach that includes a focus on human subjects with a simple phenotype. Combining input from different clinical and experimental fields and databases, CPR generates reliable data in the analyses of multiple subject characteristics by advanced bioinformatic methods (computational/biological) in a continuous feedback loop (12) (**Figure 1**).

In summary, Nadkarni et al. (6) are to be congratulated on a well-designed and elegantly reported original analysis. The data they present certainly contributes to further understanding the influence of race on *APOL1* and BP in the pathogenesis of hypertension and renal disease.

ADDRESS FOR CORRESPONDENCE: Dr. Camilo Fernandez, HeartGEN Institute, 50 Staniford Street, Boston, Massachusetts 02114. E-mail: cfernan@heartgen.org.

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