The influence of race on the association of genetic variants with pathological phenotypes is an intriguing issue, and the study by Goldenberg et al. published in the present issue of Hypertension stimulates several considerations. The concept of “race” itself is the object of major controversy between those claiming that there is no biological basis for it and others supporting the scientific validity of pragmatic racial categorizations, such as that proposed by the Office of Management and Budget in the United States. Without fear of appearing “politically incorrect,” we should admit that the analysis of a large set of genetic markers has convincingly shown that ≈10% of total genetic variation in humans originates from differences between a limited number of population groups, corresponding to “geographic clusters” of individuals.2

Race or, perhaps better, ancestry-related genetic variability, may underlie different genetic risk for 2 main reasons: (1) a susceptibility variant has different frequencies in individuals of different geographic ancestries or (2) a genetic variant may result associated with increased risk of disease in ≥1 population but not in individuals of different geographic ancestries. As a general consideration, a relevant proportion of genetic polymorphisms have a substantially different frequency in different population groups; in particular, common single nucleotide polymorphisms are frequently not shared between black and nonblack populations.2 On the other hand, when the same susceptibility variants are present in different population groups, their biological impact is usually consistent across traditional racial groupings, as suggested by Ioannidis et al.3 in a recent analysis of genetic association studies in 43 diseases. There is, however, some evidence that the influence of gene variants on the risk for common diseases may actually differ among populations of different geographic ancestry; for example, the increased susceptibility to Alzheimer disease associated with apolipoprotein E ε4 homozygosity is largely different in subjects of African or Asian ancestry.4 Among the possible explanations, interactions with other genes and/or environmental factors or linkage disequilibrium with other causative variants that may differ among individuals from different geographic ancestries could be invoked.

Goldenberg et al.1 put forward the hypothesis that homozygosity for the T235 allele of the angiotensinogen gene may confer a different risk of recurrent coronary events in black and white subjects after hospital discharge for a first episode of myocardial infarction. After the seminal work in 1992 by Jeunemaitre et al.5 describing the association of a substitution of methionine by threonine at amino acid 235 of the angiotensinogen gene (AGT M235T) with arterial hypertension and plasma angiotensinogen levels in 2 distinct white population samples from Utah and France, hundreds of studies have further investigated the relationship between angiotensinogen gene variability and hypertension or other pathological cardiovascular phenotypes. As usual, in the field of genetic epidemiology, conflicting results have been accumulated, making it very difficult to draw any firm conclusion on the role of M235T or other polymorphisms in the predisposition to cardiovascular disease. Many reasons, including poor quality of several studies, may contribute to explain such inconsistency of results, but certainly the modest contribution of any single common genetic variant to complex phenotype expression plays a major role. An investigational tool often used to reconcile heterogeneous findings and enhance statistical power is the meta-analysis of multiple genetic association studies.6 By such a method, it has been shown recently that in white subjects, AGT M235T genotype was associated with a 5% to 10% increase in plasma angiotensinogen levels (MT versus MM and TT versus MM, respectively) and with a 10% to 20% increase of the risk of hypertension; in Asian subjects, M235T was associated with an increased risk of hypertension (30% to 60%) but not with plasma angiotensinogen, and in black subjects no association was found at all. Furthermore, no significant relationship of AGT M235T was found with the risk of ischemic heart disease or myocardial infarction, either in white or Asian subjects, and no data were available thus far in black subjects. With their study, Goldenberg et al.1 aim to focus on subjects of black ancestry. The authors seem to outline a kind of syllogism: (1) blacks have a worse outcome after an acute coronary event, (2) the prevalence of AGT T235 allele is higher in blacks, and, thus, (3) AGT T235 may contribute to the worse outcome in blacks. As a matter of fact, the results of the study offer a weak statistical support to an association of the AGT 235 TT genotype with higher frequency of recurrent coronary events in black but not in white patients.

There are, however, some aspects of this study that justify a cautious interpretation of its epidemiological and potential pharmacogenetic implications. The original Thrombogenic Factors and Coronary Events (THROMBO) Study8 did not support the first premise of the syllogism (there was no different outcome in white versus black patients), and another
recent article from this group already presented negative data for an association of AGT M235T with recurrent coronary events after myocardial infarction in the same group of patients, thus making questionable the a priori reason(s) to perform the present investigation and its conclusions. Another point raising some perplexity is the absence of any preliminary assessment of the statistical power of the study. The number of blacks is rather low as compared with white patients, and from an approximate calculation, the number of events in blacks not carrying the TT genotype should be as low as 8 (probably 4 in the hypertensive subgroup). To give a possible explanation of their findings, the authors speculate about the association of high plasma AGT with high plasma renin activity (PRA) in black AGT 235TT hypertensive subjects versus high plasma AGT with low PRA in black AGT 235TT normotensive subjects. Unfortunately, they did not measure either plasma AGT or PRA in this study, and referencing the meta-analysis by Sethi et al7 to support the concept of higher AGT levels in TT subjects is out of place, because that article, as mentioned above, and others do not provide any evidence of an association between AGT M235T and plasma AGT levels in black subjects.

In summary, racial and ethnic descriptors may well be used as “proxies” to infer genetic risk for disease or treatment response, with the awareness that several confounding genetic and environmental variables must be taken into account. In this perspective, further association studies in different population groups, supported by reasonable working hypotheses and of adequate statistical power, may contribute to a better definition of an individual’s health profile.

Disclosures

None.

References


Geographic Ancestry, Angiotensinogen Gene Polymorphism, and Cardiovascular Risk
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