As for the writers’ concern about the nature of the causal inference made, we noted in our report that the polymorphism in question is not a functional change and therefore cannot be causal. Our primary analysis considered only resting energy expenditure, not obesity. Our secondary (ie, exploratory) analysis examined adiposity, not obesity. Hence, we refute the assertion that we made a “causal inference” regarding obesity. Nowhere do we “conclude” that the UCP3 genotype is a “cause” of differential racial susceptibility to obesity. Any connection made with racial differences in obesity appears only in our speculative discussion at the end of a report in which no conclusions were drawn.

In any genetic study, the definition of phenotype is critical. In our analysis, the phenotype was resting energy expenditure, not obesity or body mass index. Cooper and Luke seem to suggest that this is not the “phenotype of interest.” We strongly disagree, because we believe that attempts to understand differences in resting energy expenditure will lead to a better understanding of the metabolic aspect of the energy balance equation.

We agree with Cooper and Luke on the crucial role that lifestyle plays. In fact, our concluding statement is, “...the high prevalence of obesity in African American women in the United States today may be the result of their contemporary lifestyle of relatively high energy intake and physical inactivity in the presence of an underlying genetic propensity for efficient energy conservation.”

Finally, Cooper and Luke are mistaken in their assertion that we have longitudinal data on resting energy expenditure and weight change. We have data on resting energy expenditure at only one time point, when the study subjects were aged 18–21 y.

We hope that this response fully addresses and helps clarify some of the issues raised by Cooper and Luke.

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REFERENCE

Reply to R Cooper and A Luke

Dear Sir:

We thank Cooper and Luke for pointing out that there are some statistical limitations to the study by Kimm et al (1), but we believe that Kimm et al have made an important first report by identifying a gene that may underlie differences between African Americans and whites with regard to energy expenditure. Furthermore, we believe that these statistical limitations can be mostly discounted because the association between uncoupling protein 3 (UCP3) and UCP2 alleles and metabolic rate has already been replicated in at least 2 other studies (2, 3). Although differences between studies preclude conclusions about the roles of specific polymorphisms in racial differences, other investigators have reported differences in allelic frequencies and association between African Americans and whites for alleles for UCP2 and UCP3 (4). We have numerous other differences of opinion with Cooper and Luke on topics not reviewed by Kimm et al (1) or Schonfeld-Warden and Warden (5).

Before discussing these specific issues, we would like to point out that neither Kimm et al nor the accompanying editorial (5) suggested that a G→T single-nucleotide polymorphism (SNP) in exon 5 of UCP3 caused metabolic and obesity effects. Rather, both publications suggest that this SNP might be linked with other alleles that do have such effects. This suggestion is consistent with recent reports of differences between African Americans and whites in the sizes and numbers of haplotype blocks. Haplotype blocks are sizable genomic regions for which there is little evidence for historical recombination and within which only a few common haplotypes (linked SNPs on the same chromosome) are observed (6). The authors of a recent study stated, “We estimate that half of the human genome exists in blocks of 22 kb or larger in African and African-American samples and in blocks of 44 kb or larger in European and Asian samples. Within each block, a very small number of common haplotypes (3 to 5) typically capture 90% of all chromosomes in each population. Both the boundaries of blocks and the specific haplotypes observed are shared to a remarkable extent across populations. The main variation is a subset of alleles (haplotypes and recombinant forms) that are observed only in samples with more recent African ancestry” (6). Thus, it is possible (likely) that the SNP genotyped by Kimm et al in exon 5 of UCP3 is a member of a smaller or different haplotype block in African Americans than in whites. The immediate implication is that the UCP3 exon 5 SNP may be providing different information about adjacent SNPs and adjacent genes, such as UCP2, in African Americans than in whites.

Our first specific difference of opinion with Cooper and Luke concerns the roles of UCP3 and UCP2 in causing obesity. In their first sentence, they stated, “We disagree with the conclusions about the uncoupling protein 3 gene (UCP3) as a genetic determinant of susceptibility to obesity in blacks and whites that were put forward by Kimm et al in their report in a recent issue of the Journal … and in the accompanying editorial ….” A recent review of the literature (7) identified multiple independent studies with significant associations of UCP2 and UCP3 alleles with obesity. Many of these studies reported such low P values for the association of UCP2 or UCP3 alleles with obesity phenotypes that the P values remain highly significant even after correction for multiple testing. Several (but not all) alleles in both UCP2 and UCP3 have been associated with obesity (usually body mass index but sometimes also fat mass) in several different ethnic groups, including Europeans, Indians, Asians, and African Americans (7). Thus, although no monogenic obesity disorders have been attributed to mutations of UCP3 or UCP2, current evidence is strongly consistent with the hypothesis that one or both influence the development of human obesity.

Our second disagreement with statements made by Cooper and Luke concerns the relation of energy expenditure to obesity. We agree that a
causal relation between metabolic rate and obesity is likely, but it has not been unambiguously shown. However, Cooper and Luke stated, “It would have been more instructive to know whether a relation exists between RMR and obesity before concluding that a causal connection exists between an SNP in UCP and the differences between blacks and whites in susceptibility to obesity.” They appear to assume that alleles of UCP2 and UCP3 could influence obesity only by altering the metabolic rate, but the associations of UCP2 and UCP3 with human obesity do not make any assumptions about the underlying mechanisms. For instance, Horvath et al (8) stated, “Mitochondrial uncoupling protein 2 (UCP2) is expressed discretely in (hypothalamic) neurons involved in homeostatic regulation. UCP2 protein was associated with the mitochondrial fatty acid transport (9). The association of exon 5 alleles of UCP3 with metabolic rate may directly influence obesity. However, this association may simply be correlated with other changes that also have functional effects on obesity.

Finally, Cooper and Luke stated, “…there are other, much more plausible explanations for the differences in obesity among the various ethnic or racial groups in the United States.” We agree that environment and socioeconomic status are important influences on obesity. However, the data of Kimm et al suggest that the UCP3 genotype has a divergent influence on metabolic rate within a single ethnic group. This does not alter the observation that environment is important—it simply suggests a new dimension to the problem.

Our overall model is that UCP2 and UCP3 are known obesity genes with significant effects on population variance. They may influence obesity by altering the metabolic rate (10). Alleles of exon 5 UCP3 may be associated with differences in obesity between African Americans and whites because these alleles may be part of divergent haplotype blocks that include alleles with divergent effects on metabolic rate and obesity in these 2 ethnic groups. Obesity in other ethnic groups, such as Hispanics, may be due to other genes or alleles—the data of Kimm et al provide no information about the underlying causes of other racial differences in obesity. Thus, the identification by Kimm et al of a gene and an SNP that may influence energy expenditure in African Americans but not in whites is an important beginning that needs replication but that is fully consistent with a much larger literature from many independent investigators.

REFERENCES

Erratum


In the first sentence of the penultimate paragraph on page 906, the word linolenic should be replaced with linoleic. The sentence should read as follows: Furthermore, the rate of conversion of ALA to long-chain fatty acids is dependent on the concentration of linoleic acid (7).