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Letters to the Editor

RE: "DO WE NEED GENOMIC RESEARCH FOR THE PREVENTION OF COMMON DISEASES WITH ENVIRONMENTAL CAUSES?"

Khoury et al. (1) nicely reviewed some of the reasons why studying the genetic component of complex disease etiology might be useful. We agree in principle that epidemiologic research should continue to investigate both the genetic and nongenetic determinants of common disorders. However, we do not believe that the arguments of Khoury et al. invalidate Merikangas and Risch's (2) thesis that genetic research for diseases appearing to be highly amenable to environmental modification should be of lower priority than genetic research for diseases that have an implicated genetic basis but which cannot now be treated or prevented with environmental changes. Berrettini et al. (3) commented further on this thesis in their letter in *Science* published recently.

In essence, Khoury et al. state that even for those complex diseases for which intervening upon environmental risk factors is known to be useful, potential genetic characteristics are also worth studying *because of* the existence of gene-environment interactions. These interactions may amplify the public health benefits of focusing interventions on those individuals with the highest combined genetic and environmental risks.

The crucial issue therefore is how important gene-environment interactions can reasonably be expected to be. Stating that ''almost all human diseases result from interactions between genetic variants and the environment'' (1, p. 800) does not address the problem. It suggests that gene-environment interactions may play a large role in the etiology of complex traits, that is, that the environmental effect is much larger in those carrying the deleterious genetic traits than in those who don't. Yet, where is the evidence supporting this? Khoury et al. indicate areas of potential interest, such as family-centered interventions, but whether this will improve prevention strategies for common diseases remains to be demonstrated.

In a recent study based on careful measurement of 10 environmental exposures and 275 single nucleotide polymorphisms from 11 genes involved in the reverse cholesterol transport pathway, we found that a much larger fraction of the population variance in high density lipoprotein cholesterol was explained by body mass index rather than by the genetic variants (4). This was of course expected as the rapid changes in hypercholesterolemia, body mass index, and diabetes observed over the last 10 years could not plausibly have arisen from genetic causes (5). However, the very modest role of gene-environment interactions in explaining the variation in high density lipoprotein cholesterol was still very surprising. Indeed, the nongenetic (E) and genetic (G) main effects explained 28 percent and 4 percent, respectively, of the high density lipoprotein cholesterol variance, while the fraction explained by the *combined* effects of G × G, E × E, and G × E interactions was only 2 percent.

We do not pretend that our study provides the final word on the question. In fact, there is plenty of room for speculation as to why we may have underestimated the importance of interactions. On the other hand, there is very little published evidence that contradicts our findings. It appears therefore premature to argue that it is *because of* gene-environment interactions that Merikangas and Risch's thesis should be rejected. Consider again the current obesity epidemic. Its extremely rapid worldwide progression and the fact that no ceiling prevalence of obesity has been observed in any population do not rule out a major role of gene-environment interactions but tend to speak against it.

Epidemiologic research still needs to establish whether complex human diseases result *substantially* from interactions between genetic variants and the environment. While this objective certainly warrants more genetic-environmental research, it should not be taken for granted that the eventual findings will have great public health relevance, and the quest should not delay implementing public health interventions on environmental factors at the population level.

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