The Author's Reply

To the Editor: We thank Dr. Schaer for his interesting suggestion. Our results point to an association between functionally distinct phenotypes of the haptoglobin gene product and the nephropathy endpoint. Linkage disequilibrium is the result not only of physical proximity of loci, but also of many other factors related to the evolutionary history of nucleotide diversity in the region. The mutational event leading to the polymorphism we have used has been dated at approximately 100 000 years before the present, and the allele frequencies differ in different populations as expected. In order for the association that we have reported to reflect an association based on linkage disequilibrium with the LCAT gene, it would be necessary to define the relevant polymorphisms in the LCAT gene and/or establish the pattern of linkage disequilibrium across the whole region in multiple populations, based on the generation of haplotypes.

Ultimately, as pointed out by Dr. Schaer's definitive demonstration of the importance of the haptoglobin polymorphism or any other polymorphism, studies of diabetic nephropathy in transgenic animal models expressing the different polymorphic proteins must be done. In addition we await a better understanding of the biochemical differences between the different polymorphic forms of the protein and the relevance of these differences in the development of diabetic nephropathy.

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