COMMENTS AND RESPONSES

Prognostic Value of the Insertion/Deletion Polymorphism of the *ACE* Gene in Type 2 Diabetic Subjects: Results From the Non-Insulin-Dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril (DIABHYCAR), Diabete de type 2, Nephropathie et Genetique (DIAB2NEPHROGENE), and Survie, Diabete de type 2 et Genetique (SURDIAGENE) Studies

Response to Hadjadj et al.

Hadjadj et al. (1) have recently reported on the potential prognostic value of the *ACE* insertion/deletion (ACE I/D) polymorphism in their study of Caucasians with type 2 diabetes. The ACE II genotype contributed to the development of end-stage renal failure (ESRF) in their main cohort analyses of patients from the Non-Insulin-Dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril (DIABHYCAR) study ($P = 0.034$) (1). This finding was somewhat surprising because the II genotype, which has been linked to lower serum ACE levels, has previously been associated with protection against diabetic nephropathy (2,3). Particularly, a meta-analysis of 47 studies comprising 14,727 subjects found evidence for such a protective effect (2), a finding that has been reiterated in a more recent update of that meta-analysis (3).

Regarding the present unexpected finding by Hadjadj et al., it should be realized that their finding was based on only 18 cases that had developed ESRF during a 4-year follow-up of 3,126 patients (1). Critically, this finding failed to be confirmed in the replication studies on patients from the Survie, Diabete de type 2 et Genetique (SURDIAGENE) and Diabete de type 2, Nephropathie et Genetique (DIAB2NEPHROGENE) studies that had also been included in their report (1). In retrospect, this lack of replication probably highlighted a need for a larger number of incident cases in their main cohort analyses.

It is also worth noting that attention was not given to another emerging aspect of ACE genetic variation, i.e., haplotype diversity at this locus. Findings from recent reports have provided encouragement for an extensive haplotype analysis beyond the mere consideration of ACE I/D (4,5). This point was initially proposed in a study of Caucasians with type 2 diabetes from the Joslin Clinic in Boston (4): we found that although ACE I/D alone did not demonstrate any significant association with advanced diabetic nephropathy (as defined by the presence of proteinuria, chronic renal failure, or ESRF) due to the known minor effect of the II genotype (2,3), haplotype analysis of tagging single nucleotide polymorphisms in combination with ACE I/D revealed otherwise (4). Reassuringly, this evidence for a haplotype-disease association could be subsequently corroborated in a case-control study of type 1 diabetic Caucasians, albeit using a different set of single nucleotide polymorphisms for capturing haplotype diversity (5). In the context of the study by Hadjadj et al. (1), a current lack of enabling technology that allows accurate and convenient phasing of haplotypes in unrelated individuals would understandably have explained the absence of such data in their report. Such accurate haplotypic information for each individual patient would have been most useful in the survival analysis of cohorts. A comparison of the estimated haplotype frequencies between patients who progressed to ESRF and those who did not may also be meaningful.

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