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 Ng et al.

SAMY HADJADJ, MD, PHD[1,2]
RONAN ROUSSEL, MD, PHD[3,4,5]
MICHEL MARRE, MD, PHD[3,4,5]
FOR THE DIABHYCAR, DIAB2NEPHROGENE, AND SURDIAGENE STUDY GROUPS

Doctor Daniel P.K. Ng (1) was surprised by our reporting of a higher incidence of end-stage renal failure (ESRD) among the participants of the Non-Insulin-Dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril (DIABHYCAR) study with the ACE II genotype than among those without the genotype given that he had published a large, case-control–based meta-analysis supporting the idea that this genotype protects people with diabetes against the risk (2). We were surprised as well, and we were not able to replicate the results in another prospective follow-up study of type 2 diabetic subjects (the Survie, Diabete de type 2 et Genetique [SURDIAGENE] study). Our report highlights two notions regarding potentially harmful genotypes and ESRD: first, the need to replicate one finding for validation, and second, the interest of assessing the value of genotype on a prospective, follow-up basis. We noticed in DIABHYCAR that prior myocardial infarction was more frequent in the ACE II participants at baseline, whereas this genotype protected against death after myocardial infarction during the study (3). Thus, the *ACE* insertion/deletion (I/D) genotype may not be neutral for type 2 diabetic subjects. Risk of death is much higher than risk of ESRD for these subjects (4). Interestingly, Parving et al. noticed a high proportion of II genotypes among the black participants in a study on renal prognosis, whereas this genotype is infrequent in that ethnicity (5).

Ng also suggested that the haplotype-based genetic structure should be studied. We agree with this proposal, although the I/D polymorphism proved to be as informative as the haplotype-based approach in type 1 diabetic patients (6). Finally, our study focused on the *ACE* I/D polymorphism because it is the most widely studied in diabetic renal complications. We thus developed a practical evaluation of its associations.

From the [1]Centre Hospitalier Universitaire Poitiers, Endocrinology, Diabetology and Université de Poitiers, Faculté de Médecine et Pharmacie, Poitiers, France; [2]INSERM, U927, Poitiers, France; [3]INSERM, U695, Xavier Bichat Faculty of Medicine, Paris, France; the [4]Unité de Formation et de Recherche Médecine Xavier Bichat, Université Paris seven Diderot, Paris, France; and [5]Assistance Publique-Hôpitaux de Paris, Hôpital Bichat, Endocrinologie-Diabetologie-Nutrition, Paris, France.
Corresponding author: Samy Hadjadj, s.hadjadj@chu-poitiers.fr.
DOI: 10.2337/dc08-1229

References

1. Ng, DPK: 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. (Letter). *Diabetes Care* 31:e78, 2008. DOI: 10.2337/dc08-1091
2. Ng DP, Placha G, Choo S, Chia KS, Warram JH, Krolewski AS: A disease haplotype for advanced nephropathy in type 2 diabetes at the ACE locus. *Diabetes* 55: 2660–2663, 2006
3. Hadjadj S, Fumeron F, Roussel R, Saulnier PJ, Gallois Y, Ankotche A, Travert F, Khalil CA, Miot A, Alhenc-Gelas F, Lievre M, Marre M: 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. *Diabetes Care* 31:1847–1852, 2008
4. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR: Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int* 63:225–232, 2003
5. Parving HH, de Zeeuw D, Cooper ME, Remuzzi G, Liu N, Lunceford J, Shahinfar S, Wong PH, Lyle PA, Rossing P, Brenner BM: ACE gene polymorphism and losartan treatmentin type 2 diabetic patients with nephropathy. *J Am Soc Nephrol* 19: 771–779, 2008
6. Hadjadj S, Tarnow L, Forsblom C, Kazeem G, Marre M, Groop PH, Parving HH, Cambien F, Tregouet DA, Gut IG, Theva A, Gauguier D, Farrall M, Cox R, Matsuda F, Lathrop M, Hager-Vionnet N: Association between angiotensin-converting enzyme gene polymorphisms and diabetic nephropathy: case-control, haplotype, and family-based study in three European populations. *J Am Soc Nephrol* 18:1284–1291, 2007