COMMENTS AND RESPONSES

Comment on: Zhang et al. Peroxisome Proliferator–Activated Receptor γ Polymorphism Pro12Ala Is Associated With Nephropathy in Type 2 Diabetes: Evidence From Meta-Analysis of 18 Studies. Diabetes Care 2012;35:1388–1393

The recently published meta-analysis by Zhang et al. (1) shows that the Ala12 variant of peroxisome proliferator–activated receptor γ is a significantly protective factor for diabetic nephropathy. This association was observed in Caucasians, but no similar association was shown in Asians. The absence of a significant effect in the Asian subgroup was explained by the authors by the low frequency of the Ala12 allele in the Asian populations leading to insufficient statistical power. Gene-gene and gene-environmental interactions have been indicated as additional explanations for the ethnic difference.

However, the conflicting results obtained could be in part explained by a survival bias, which can substantially attenuate the underlying risk associated with genetic polymorphism in case-control studies (2). A survival bias occurs when there is a greater exclusion of cases in the high-risk genotype due to reduced survival: the decline in the odds will correspond to a reduction in statistical significance. In this case, nephropathy is much more prevalent in Asians than in Caucasians (3,4), and it is also a well-recognized risk factor for mortality in persons with or without diabetes. It is possible that among others, a differential survival bias in Asians and Caucasians could further contribute to the conflicting results leading to a dilution of the association between nephropathy and Pro/Pro genotype particularly strong in Asians. Prospective studies can avoid survival bias by including all incident cases during follow-up, including fatal cases. All the studies included in the meta-analysis of Zhang et al. are cross-sectional. The only exception is the study by De Cosmo et al. (5), which shows that the Ala allele protects from worsening albuminuria and new-onset microalbuminuria. These results were obtained in the setting of an intervention trial evaluating the effect of treatment with ACE inhibitors on new onset microalbuminuria. Further prospective studies, particularly in the context of real practice, are needed to confirm this protective effect in different ethnic groups, to assess whether the putatively protective effect of the Pro12 Ala polymorphism may translate into a reduced long-term risk of renal and cardiovascular events.

Emanuela Lapice, phd
Sara Cocozza, md
Gabriele Riccardi, md
Olga Vaccaro, md

From the Department of Clinical and Experimental Medicine, Federico II University of Naples, Naples, Italy.
Corresponding author: Emanuela Lapice, emanuela1978@hotmail.it.
DOI: 10.2337/dc12-1993

Acknowledgments—No potential conflicts of interest relevant to this article were reported.

References

1. Zhang H, Zhu S, Chen J, et al. Peroxisome proliferator–activated receptor γ polymorphism Pro12Ala is associated with nephropathy in type 2 diabetes: evidence from meta-analysis of 18 studies. Diabetes Care 2012;35:1388–1393
2. Williams P, Pendyala L, Superko R. Survival bias and drug interaction can attenuate cross-sectional case-control comparisons of genes with health outcomes: an example of the kinesin-like protein 6 (KIF6) Trp719Arg polymorphism and coronary heart disease. BMC Med Genet 2011;12:42
3. Lu B, Wen J, Song XY, et al. High prevalence of albuminuria in population-based patients diagnosed with type 2 diabetes in the Shanghai downtown. Diabetes Res Clin Pract 2007;75:184–192
4. Liu L, Zheng T, Wang F, et al. Pro12Ala polymorphism in the PPARG gene contributes to the development of diabetic nephropathy in Chinese type 2 diabetic patients. Diabetes Care 2010;33:144–149
5. De Cosmo S, Motterlini N, Prudente S, et al.; BENEDICT Study Group. Impact of the PPAR-gamma2 Pro12Ala polymorphism and ACE inhibitor therapy on new-onset microalbuminuria in type diabetes: evidence from BENEDICT. Diabetes 2009;58:2920–2929