Haiyu Tang and Chuanyu Gao

COMMENT ON THE LOOK AHEAD RESEARCH GROUP

Prospective Association of *GLUL* rs10911021 With Cardiovascular Morbidity and Mortality Among Individuals With Type 2 Diabetes: The Look AHEAD Study. Diabetes 2016;65:297–302

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The Look AHEAD (Action for Health in Diabetes) Research Group (1) found that the C allele for rs10911021 was closely related to the primary composite end point of cardiovascular death and that intensive lifestyle intervention did not affect this correlation. Therefore, the authors concluded that rs10911021 was strongly linked to the morbidity and mortality of cardiovascular disease (CVD) in patients with type 2 diabetes. Similar conclusions have been made by Qi et al. (2) and Prudente et al. (3). We believe rs10911021, as an important single nucleotide polymorphism, may be a potential genetic target to turn the principles of vascular complications of diabetes from late treatment to early prevention, as the fact that its correlation with CVD appears in the diabetes population (2) and that it is not correlated with CVD in patients without diabetes, which eliminates numerous traditional risk factors of CVD.

In addition, despite the description of rs10911021 as "a single nucelotide polymorphism (SNP) upstream of the glutamate-ammonia ligase gene (*GLUL*)," statements such as "a glutamate-ammonia ligase gene (*GLUL*) polymorphism" and "*GLUL* rs10911021" (1) may give a false impression that rs10911021 exists in *GLUL*, which in our opinion is inappropriate. Actually rs10911021 is situated not in the *GLUL* coding region but in a noncoding sequence upstream of *GLUL*, a distance of about 200,000 bp. This fact warns that epigenetic mechanisms may exert a pivotal effect on the pathogenesis of CVD (4) because the noncoding sequence upstream of the *GLUL*, where rs10911021 is situated, may be translated into a microRNA, long noncoding RNA, or circular RNA to play its key role. Since ancient times, it has been a key point of dispute as to whether expression and regulation matters more in the deep mechanism of CVD (5).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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Department of Cardiology, Henan Provincial People's Hospital, Zhengzhou, China
Corresponding author: Chuanyu Gao, gaocy6802@163.com.