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RESPONSE TO 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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We thank Drs. Tang and Gao for their letter (1) in response to our article (2) describing the association of rs10911021 with cardiovascular disease (CVD) in overweight/obese participants with type 2 diabetes in the the Look AHEAD (Action for Health in Diabetes) trial. Their letter questioned whether it was appropriate for our study to ascribe the association of rs10911021 with CVD on the basis of allelic differences in the glutamate-ammonia ligase gene (*GLUL*) located ~200,000 bp away from this intergenic single nucleotide polymorphism (SNP). It is important to emphasize that our study was not designed to address the mechanistic basis of the association of rs10911021 with CVD. Rather, our goal was to replicate the findings of Qi et al. (3) and to determine whether a lifestyle modification altered the association of this SNP with the primary and secondary outcomes of the Look AHEAD trial. We sincerely hope that our article confirming the association of rs10911021 with cardiovascular end points will inspire molecular geneticists to define the mechanism(s) by which this SNP is associated with CVD in patients with diabetes. Epigenetic mechanisms might explain this association. We also feel it is also important to emphasize that based on the current literature it is appropriate to consider rs10911021 to be reflective of *GLUL* because Qi et al. (3) described the association of this variant with

the ratio of serum pyroglutamic-to-glutamic acid and that the association of rs10911021 with CVD was shown to be weakened by the adjustment for the serum pyroglutamic-to-glutamic acid ratio (3). We hope future mechanistic studies will clarify the mechanism by which rs10911021 is associated with CVD; however, given the available evidence, we feel that it is appropriate to consider that the effects of rs10911021 are, at least in part, mediated through the *GLUL* gene.

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

## References

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3. Qi L, Qi Q, Prudente S, et al. Association between a genetic variant related to glutamic acid metabolism and coronary heart disease in individuals with type 2 diabetes. *JAMA* 2013;310:821–828

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