RESPONSE TO COMMENT ON DAWED ET AL.

Genome-Wide Meta-analysis Identifies Genetic Variants Associated With Glycemic Response to Sulfonylureas. Diabetes Care 2021;44:2673–2682

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We appreciate the opportunity to respond to the letter by Wang et al. (1) regarding our article in a recent issue of *Diabetes Care* (2). In responding to the authors' critique, we should first say that pharmacogenomic research has long been constrained by the unavailability of longitudinal data large enough to achieve the statistical power required to detect variants associated with drug response. To address this, our study aimed to maximize statistical power by combining data from the largest number of samples for sulfonylurea response available from six centers within the Metformin Genetics Plus Consortium (MetGen Plus) and the DIabetes REsearCh on patient straTification (DIRECT) consortium.

We agree with Wang et al. (1) that there is no definitive in vivo study on the role of OATP1B1 in the transport of sulfonylureas. Currently, in vivo evidence comes from the use of a single dose of rifampicin, a nonselective OATP1B1/1B3 inhibitor, which results in increased levels of glyburide (3). We support our genome-wide association studies findings with in vitro studies by showing that glipizide and glyburide are substrates of OATP1B1. The authors pointed out that we have not done the same for gliclazide. However, this was previously investigated by Yang et al. (4), who showed that gliclazide is also a substrate for OATP1B1 but not an inhibitor of the transporter (5).

The authors were unable to replicate the association between rs10770791 genotype and glycemic response to sulfonylureas using data from the Hong Kong Diabetes Register. However, the outcome definition between these studies is not identical. While we defined glycemic response as a linear reduction in HbA_{1c} after 12 months of stable sulfonylurea treatment, Wang et al. (6) used

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treatment failure as defined by *1*) switching to or addition of a second or third glucose-lowering drug, including insulin, for more than 6 months or *2*) two consecutive measurements of HbA_{1c} $\geq$8.5% (3–12 months apart during treatment) and a dichotomized outcome defined as achieving HbA_{1c} <7% within 18 months of treatment without experiencing treatment failure. This makes comparison between the studies difficult. HbA_{1c} reduction is a continuous trait, and dichotomizing response phenotypes can be misleading and should be avoided (7). The authors did not show a significant association between *SLCO1B1*15* and achieving target HbA_{1c} <7% (n = 1, 042). In contrast, we have shown an association between rs4149056 (**5*; V174A) ($\beta = 0.10 \pm 0.03\%$, $P = 2.72 \times 10^{-4}$) and rs2306283 (**1B*; N130D) ($\beta = 0.08 \pm 0.02\%$, $P = 4.32 \times 10^{-5}$) using HbA_{1c} reduction as a continuous trait. However, in a conditional analysis with rs4149056, only rs10770791 remained strongly associated with sulfonylurea response. Results for rs10770791 conditioned by any of the known nonsynonymous single nucleotide polymorphisms in the Hong Kong Diabetes Register are not provided; thus, direct comparison between the two studies is even more difficult.

Finally, the differences in the findings from our two studies could result from a population-specific genetic effect. Well-powered studies with harmonized methodologies across different ethnic groups are required.

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