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 read with interest the article by Dawed et al. (1) reporting genetic variants associated with sulfonylurea response in a genome-wide meta-analysis of White Europeans. The C allele of rs10770791 in the intronic region of solute carrier organic anion transporter family member 1B1 (*SLCO1B1*) was identified as one of two loci associated with improved HbA_{1c} response. Interestingly, two well-established nonsynonymous variants of *SLCO1B1*, rs4149056 (**5*, c.521T>C, p.V174A) and rs2306283 (**37*; c.388A>G, p.N130D), in partial link disequilibrium with rs10770791, were not significantly associated with sulfonylurea response based on individual-level data (n = 3,557).

Although in vitro data implicate sulfonylureas as substrates of organic anion transporting polypeptide 1B1 (OATP1B1) transporter, there is a lack of in vivo data supporting an effect of *SLCO1B1* variants on sulfonylurea pharmacokinetics. This contrasts with statins, where the rs4149056 c.521T>C allele is well known to be associated with a 4.6-fold increase in risk of statin-induced myopathy. This is supported by both in vitro evidence of reduced OATP1B1 transporter activity and in vivo pharmacokinetic studies showing higher statin exposure among CC homozygotes (2). Further, Dawed et al. (1) only investigated the role of OATP1B1 in up-take of glipizide and glyburide, but not of gliclazide—the sulfonylurea used by 90% of the Genetics of Diabetes Audit and Research in Tayside Scotland (GoDARTS) cohort (40% of the total study population). Sulfonylureas with different chemical structures might be expected to interact differently with transporters.

Considering ethnic differences in the frequency of *SLCO1B1* variants (3), we considered their associations with sulfonylurea response in Chinese individuals with type 2 diabetes in the Hong Kong Diabetes Register. We recently reported *CYP2C19* loss-of-function polymorphisms were associated with lower risk of sulfonylurea failure and improved treatment response among 2,341 incident users (4). In our cohort, the rs10770791 T allele was the minor allele, with a minor allele frequency of 22%. In the study by Dawed et al. (1), the T allele was regarded as the noneffective allele and associated with reduced HbA_{1c} response. We found no difference in risk of sulfonylurea treatment failure in rs10770791 CT (adjusted hazard ratio [aHR] 0.95, 95% CI 0.85–1.05, n = 833) and TT (aHR 0.95, 95% CI 0.79–1.16, n = 145) genotypes versus the CC wild type (n = 1,312). This was following adjustment for age, sex, diabetes duration, baseline HbA_{1c}, BMI, treatment group, and average sulfonylurea daily dose. Similarly, no differences were observed in the early HbA_{1c} response within 18 months by rs10770791 genotype. Conversely, the *SCLO1B1*15* haplotype (containing both rs4149056 and rs2306283 variants) tended to be associated with higher odds of reaching HbA_{1c} <7% (adjusted odds ratio 1.88, 95% CI 0.96–3.70, P = 0.068) versus **1A*, although the association was nonsignificant.

The discovery of a novel variant located within *SLCO1B1* might provide novel insights into the role of drug transporter OATP1B1 in sulfonylurea response, with potential implications for drug–drug–gene interactions with other OATP1B1 substrates (e.g., statins) and more potent OATP1B1 inhibitors (e.g., gemfibrozil). These reciprocal interactions may influence the risk of adverse drug reactions from both drugs, such as severe hypoglycemia due to sulfonylureas as well as statin-induced myopathy. The difference in minor allele frequency and haplotype structures between different ethnicities calls for independent replication in other cohorts, and also with different drugs within the same class.

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