We appreciate the interest that Zhang et al. (1) expressed in our article (2), in which we suggested that persons with a D allele (H63D) in the hemochromatosis gene (HFE) may have a moderately increased risk of type 2 diabetes mellitus. Zhang et al. (1) commented that some of the data presented in our article were not consistent with the data in the original papers. In addition, they discussed the choice of genetic models and the credibility grade of our findings.

First, we checked our data carefully and recalculated the odds ratios and 95% confidence intervals. For the H63D variant, the odds ratio for type 2 diabetes mellitus was modestly increased for persons carrying a D allele compared with those with an H allele (odds ratio (OR) = 1.11, 95% confidence interval (CI): 1.00, 1.22; \( P = 0.04 \)). For the C282Y variant, the risk for type 2 diabetes mellitus was not significantly increased for participants carrying a Y allele compared with those with a C allele (OR = 1.00, 95% CI: 0.85, 1.18; \( P = 0.99 \)). In addition, no significantly increased risk was observed in people with a homozygous or heterozygous variant compared with those with a wild genotype (OR = 1.10, 95% CI: 0.99, 1.23; \( P = 0.08 \)).
inconsistency of the data shown in our Table 3 with the data from original reports and Zhang et al. (1) partly resulted from the confusing data in original studies and different ways of dealing with the original data. For the study by Florkowski et al. (3) (reference 25 in our paper), we noticed that the total number of type 2 diabetes mellitus cases in their Table 1 did not match the sum of the number in each genotype category. Therefore, we excluded this study from our meta-analysis. For the study by Campo et al. (4) (reference 29 in our paper), we noticed that the total number of type 2 diabetes mellitus cases in their Table 1 did not match the sum of the number in each genotype category. Therefore, we excluded this study from our meta-analysis. For the study by Qi et al. (5) (reference 36 in our paper), the numbers of cases with the HH genotype in their Tables 2 and 3 were inconsistent (i.e., 498 vs. 489, respectively). After careful calculation, the correct number of patients with the HH genotype should be 498. We are sorry for not identifying Qi et al.’s error in a timely fashion and appreciate the comments from Zhang et al. Moreover, the study by Hegele et al. (6) treated both type 2 diabetes mellitus patients and persons with impaired glucose tolerance as cases, and we excluded this study. Data extracted from the other included studies can be traced in our meta-analysis (2).

Second, we appreciate the comments from Zhang et al. (1) with regard to the choice of genetic models that was not involved in our article. Until now, the selections of genetic models of inheritance for the associations of common single nucleotide polymorphisms with diseases remain unclear. Salanti et al. (7) found that the additive model of inheritance was appropriate for diabetes by a Bayesian meta-analysis approach. In our article (2), the odds ratios of the additive model (D allele vs. H allele) and the dominant model (DD + HD vs. HH genotype) were 1.11 (95% CI: 1.00, 1.22) and 1.10 (95% CI: 0.99, 1.23), respectively. Therefore, the additive model (log(OR_{DD/HH}) = 0.04, 95% CI: −0.01, 0.08; log(OR_{DD/HH}) = 0.12, 95% CI: −0.02, 0.26; \lambda = \log(OR_{DD/HH})/\log(OR_{DD/HH}) = 0.33) was recommended for random-effect logistic regression models.

Third, we agree that the effect sizes observed in our study were small or very small, according to the proposed credibility grade of molecular evidence for complex diseases (8).