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Response to Invited Commentary

Miyaki et al. Respond to "Gene × Lifestyle Interactions"

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We appreciate the thorough commentary by Drs. Franks and Nettleton (1). The major finding of our paper (2) was that interaction between the cyclin-dependent kinase 5 regulatory subunit-associated protein 1-like 1 (*CDKAL1*) gene and total energy intake (TEI) affected hemoglobin A_{1c} levels in apparently healthy Japanese men. Given the limited space in which to respond to Franks and Nettleton, we will focus on a few of the more pertinent issues.

First, we are aware of the limitations of our study, including its low statistical power due to the small sample size, and we agree with Franks and Nettleton regarding the consequences of a low-powered study in general. These consequences can only be overcome by selecting a larger cohort. Thus, our paper is, at best, an exploratory analysis rather than a validation analysis of the effect of a well-studied *CDKAL1* polymorphism.

Franks and Nettleton raised a question with regard to the accuracy of the food frequency questionnaire (FFQ) used for measuring TEI. We agree that assessing the validity of the dietary intake method is essential. The FFQ we used has been compared with 7-day dietary records and has been demonstrated to have a significant correlation with TEI (3). Thus, we believe this method allowed us to place participants into broad categories along a distribution of TEI (e.g., tertiles, as we used in the study). Body height was also taken into account as a means of reducing measurement bias in the calculation of TEI from FFQ (4). The possible measurement bias was noted as a limitation of the study in our original report (2).

Franks and Nettleton raised an issue regarding consistency, taking Hill's criteria (5) as an example and referring to 2 intervention studies (6, 7) and 1 cohort study (8) that were claimed to not support our data. One of the intervention studies (6), which Franks coauthored, involved a high-risk diabetic population, the majority of which received lifestyle intervention or medication. Significant differences exist in the characteristics of the populations, including mean body mass index, which was 34 in Franks' group and 23 in our group. The cohort study (8), also coauthored by Franks, accounted for an interaction between the gene and physical activity, dichotomized into active and inactive states by means of a computer-assisted questionnaire. Whether or how TEI was measured in this group does not seem to be explained in the paper (8). Thus, the context and aims of these studies seem to be so remote from ours that we cannot infer any indication of consistency or inconsistency.

In addition, Franks and Nettleton questioned the biologic plausibility of our findings. *CDKAL1* is involved in β-cell function, and polymorphisms within the gene have been repeatedly shown to affect blood glucose levels and insulin secretion, but not fasting glucose levels, after a glucose tolerance test (9). Therefore, we think it is reasonable to speculate on and test whether the *CDKAL1* gene × TEI interaction correlates with blood glucose levels. Here, we would like to reiterate that although we observed a correlation with hemoglobin A_{1c}, we did not observe a correlation with fasting glucose levels (2).

As for causality, Franks and Nettleton also suggested that the effect of the *CDKAL1* variant might be to modify TEI but not blood glucose level. This assertion is logically true, and to ascertain the possibility one needs to stratify the population according to blood glucose level, genotype the participants, and survey TEI under an ad lib diet.

The commentary by Franks and Nettleton provided us with an opportunity to review our own study. We agree that future studies using larger cohorts are needed to validate our novel finding that the *CDKAL1* gene × TEI interaction affects blood glucose level. Such studies may highlight other environmental or genetic interaction factors that are prerequisites for this effect.

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Conflict of interest: none declared.

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