Response to Comment on: Marquez et al. Low-Frequency Variants in *HMGA1* Are Not Associated With Type 2 Diabetes Risk. Diabetes 2012;61:524–530

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We read with surprise and disappointment the comment in *Diabetes* by Brunetti et al. (1) who made unfair comments about our negative study published in the same journal (2). Therefore, we felt the necessity to provide a point-by-point response to all raised issues.

1) In contrast to the claims by Brunetti et al. (1), we have never reported in meeting abstracts any consistent associations between *HMGA1* variants and type 2 diabetes (T2D) risk when all French samples were analyzed together. Trends observed in obese subjects were not confirmed in a larger number of individuals and BMI was finally found not to influence association with T2D susceptibility (2). Therefore, the so-called "inconsistencies" between our previous abstracts and our published study are not justified and do not question our recent findings.

2) Discrepancies in allele frequencies between our study (2) and that of Chiefari et al. (3) are unlikely to be due to different selections of control samples. In both studies, two groups of normoglycemic controls were selected, or not, based on their family history of T2D. Contrary to what was reported in Italians (3), no difference was observed between the French control group of subjects without family history of T2D and the French control group composed of individuals without specific selection criteria (c.136–14_136–13insC allele frequency: 2.82% and 2.59%, respectively) (2).

3) In our study (2), genomic DNA was directly sequenced or genotyped for the c.136–14_136–13insC variant using the high-resolution melting (HRM) method, with an estimated concordance rate of 99%. HRM was preferred for genotyping since the genotype calling of this variant using a custom Taqman assay was not satisfying. Therefore, our results were based on accurate genotypes.

4) Our expression study was not performed in T2D patients, contrary to what was reported by Chiefari et al. (3), given that glucose-lowering medications could bias the results. Instead, we analyzed the adipose tissue of Swedish individuals (c.136–14_136–13insC allele frequency: 3.30%) who share similar T2D genetic loci with other Europeans, including French subjects, as confirmed in previous genome-wide studies (4–9). If true, the strong functional effects reported in Italians (3) should have been observed in other Europeans carrying the c.136–14_136–13insC variant.

5) In our large meta-analysis comprising 16,605 T2D case subjects and 46,179 control subjects of European origin, the association of the c.136–14_136–13insC variant with T2D risk was not close to significance (odds ratio = 0.95 [0.83–1.08], $P = 0.44$) (2) in contrast to what was suggested by Brunetti et al. (1).

Replication of research findings enhances the positive predictive value of research findings being true (10). In Europeans, there is no consistent evidence showing that the c.136–14_136–13insC variant is associated with T2D risk (2). Therefore, the comments made by Brunetti et al. (1) were inappropriate since they were based on unfounded assumptions.

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